



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 45

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 45

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

ALAN R. KATRITZKY, FRS

Kenan Professor of Chemistry

Department of Chemistry

University of Florida

Gainesville, Florida



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Contents

PREFACE	vii
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Chiral Induction Using Heterocycles

EIICHI FUJITA AND YOSHIMITSU NAGAO

I. Introduction	1
II. Preparation of C4-Chiral Thiazolidine-2-thiones and Oxazolidine-2-thiones ...	2
III. Chiral Recognition in Aminolysis	4
IV. Analytical Separation and Optical Resolution of Racemic Carboxylic Acids and Amino Acids	6
V. Highly Diastereoselective Aldol-Type Reactions	7
VII. Highly Selective Nonenzymatic Chiral Induction onto Prochiral σ -Symmetric Dicarboxylic Acids	22
VII. Methylseleno-Promoted Ketene-Imine Cycloaddition Reaction	30
VIII. Conclusion	33
References	33

Heterocyclic Quinones

MIHA TIŞLER

I. Introduction	38
II. Quinones with a Condensed Four-Membered Heterocyclic Ring	39
III. Quinones with a Condensed Five-Membered Ring with One Heteroatom	39
IV. Quinones with a Condensed Five-Membered Ring with Two Heteroatoms	74
V. Quinones with a Condensed Five-Membered Ring with Three Heteroatoms ...	82
VI. Quinones with a Condensed Six-Membered Ring	84
VII. Quinones with Two Different Heterocyclic Systems Attached to the Quinone Moiety	118
VIII. Miscellaneous Heterocyclic Quinones	121
IX. Appendix	122
References	124

The Chemistry of Thiophenium Salts and Thiophenium Ylids**ALEXANDER E. A. PORTER**

I. Introduction	152
II. S-Alkylated Thiophenes	153
III. Thiophene S,C-Ylids	159
IV. Thiophene S,N-Ylids	176
V. Conclusions	182
References	182

1,4-Diazocines**HOWARD D. PERLMUTTER**

I. Scope and Nomenclature	185
II. Preparative Methods	187
III. Theoretical and Structural Studies	209
IV. Reactions	217
V. Applications	223
References	224

Recent Advances in Azomethine Ylide Chemistry**OTOHIKO TSUGE AND SHUJI KANEMASA**

I. Introduction	232
II. Generation	233
III. Cycloadditions	295
IV. Intramolecular Cycloadditions	333
V. Natural Product Synthesis	337
VI. Conclusion	343
References	344

Preface

Volume 45 of *Advances in Heterocyclic Chemistry* contains five contributions, all of which break new ground for this series. In the first article, Fujita and Nagao describe the use of heterocycles for the induction of chirality. This contribution represents an example of the way in which our subject is making itself increasingly felt throughout the whole field of chemistry. The second article, by Tişler, covers heterocyclic quinones, including the many classes in which a heterocycle is fused to a 1,2- or 1,4-benzoquinone ring.

In the third article, Porter describes the chemistry of thiophenium salts and ylids, to which he has contributed extensively. The chemistry of 1,4-diazocines is presented by Perlmutter; this article follows an earlier review by the same author on azocines in Volume 31 of *Advances in Heterocyclic Chemistry*. The final article of this volume, and the second contribution from Japan, is by Tsuge and Kanemasa and deals with recent advances in azomethine ylide chemistry.

The cumulative index updates, as announced in the preface to Volume 40, will cover Volumes 41–45 and will appear in Volume 46. This will prevent a delay in the publication of Volume 45.

ALAN R. KATRITZKY

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Chiral Induction Using Heterocycles

EIICHI FUJITA

Osaka University of Pharmaceutical Sciences, Matsubara 580, Japan

YOSHIMITSU NAGAO

Institute for Chemical Research, Kyoto University, Uji, Kyoto-fu 611, Japan

I. Introduction	1
II. Preparation of C4-Chiral Thiazolidine-2-thiones and Oxazolidine-2-thiones	2
III. Chiral Recognition in Aminolysis	4
IV. Analytical Separation and Optical Resolution of Racemic Carboxylic Acids and Amino Acids	6
V. Highly Diastereoselective Aldol-Type Reactions	7
A. Aldehydes	7
1. Outline	7
2. Synthetic Applications: Chiral Azetidinones and Virginiamycin M1	11
B. 4-Acetoxy-2-azetidinones	13
1. Outline	13
2. Synthetic Application: Carbapenems	16
C. 5-Acetoxy-2-pyrrolidinone and 6-Acetoxy-2-piperidinone	18
1. Outline	18
2. Synthetic Application: Bicyclic Alkaloids	19
VI. Highly Selective Nonenzymatic Chiral Induction onto Prochiral σ -Symmetric Dicarboxylic Acids	22
A. 3-Methylglutaric Acid	23
B. <i>meso</i> -2,4-Dimethylglutaric Acid	24
1. Outline	24
2. Synthetic Application: (+)-Prelog-Djerassi Lactonic Acid Methyl Ester	25
C. <i>meso</i> -5-Norbornen-2,3-ylene- <i>endo</i> -bis(acetic acid)	26
D. <i>cis</i> -4-Cyclohexen-1,2-ylenebis(acetic acid)	26
1. Outline	27
2. Synthetic Application: (+)-Carbacyclin	27
VII. Methylseleno-Promoted Ketene-Imine Cycloaddition Reaction	30
VIII. Conclusion	33
References	33

I. Introduction

The useful physiological activity of pharmaceuticals containing asymmetric center(s) appears almost always in only one enantiomer. Hence, an effective synthesis of the desired enantiomer with optical purity is now an important

subject in chemistry. The chiral synthon has been obtained by (1) asymmetric chemical synthesis, (2) synthesis of a racemate followed by its optical resolution, (3) chiral induction in a specific prochiral compound with enzymes or microorganisms, and (4) chemical transformation from easily available sugars, amino acids, terpenoids, and other optically active natural products.

In our laboratories, new highly selective asymmetric inductions featuring the functions of C4-chiral thiazolidines and oxazolidines were recently developed. An overview of these chiral designs, reactions, and applications will be discussed in this article.

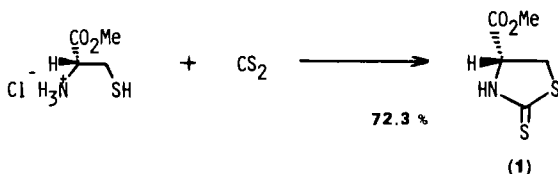
II. Preparation of C4-Chiral Thiazolidine-2-thiones and Oxazolidine-2-thiones

C4-Chiral thiazolidine-2-thiones were prepared by condensation, as, for example, (4*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione [(4*R*)-MCTT] (**1**) from L-cysteine methyl ester hydrochloride and carbon disulfide (CS₂) in the presence of triethylamine (Et₃N) in CH₂Cl₂ at room temperature (Scheme 1) (82TL201; 85JOC4072). The (4*S*)-enantiomer was similarly synthesized by using D-cysteine methyl ester hydrochloride (85CC1419).

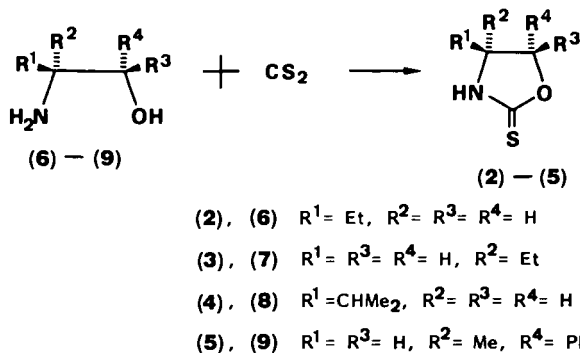
Other C4-chiral oxazolidine-2-thiones, (4*S*)- (**2**) and (4*R*)-ethyl-1,3-oxazolidine-2-thione (**3**) [(4*S*)- and (4*R*)-EOT], (4*S*)-isopropyl-1,3-oxazolidine-2-thione (**4**), and (4*R*)-methyl-(5*S*)-phenyl-1,3-oxazolidine-2-thione [(4*R*,5*S*)-MPOT] (**5**) were likewise synthesized. Typical preparations of C4-chiral 1,3-oxazolidine-2-thiones (**2**–**5**) from β-amino alcohols (**6**–**9**) are as follows.

Method A. A mixture of (2*S*)-aminobutan-1-ol (**6**) and CS₂ in the presence of Et₃N in CH₂Cl₂ was stirred at room temperature for 4 hr to give (4*S*)-EOT (**2**) in 58.4% yield (Scheme 2) (85JCS(P1)2361).

Method B. A solution of potassium hydroxide in aqueous ethanol was added to a solution of (+)-norephedrine hydrochloride and CS₂ in aqueous ethanol with stirring and ice cooling. The mixture was stirred at 70–80°C for 6 hr. The usual workup gave the desired (4*R*,5*S*)-MPOT (**5**) in 69% yield (Scheme 2) (85JCS(P1)2361).



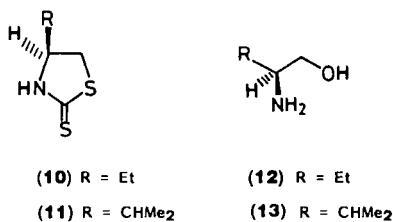
SCHEME 1



SCHEME 2

(4*S*)-Ethyl-1,3-thiazolidine-2-thione [(4*S*)-ETT] (**10**) and (4*S*)-isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT] (**11**) were prepared in 82.5 and 65.3% yield, respectively, by heating (80–90°C) a solution of the corresponding amino alcohols [(2*S*)-amino-1-butanol (**12**) and (2*S*)-amino-3-methyl-1-butanol (**13**)] in aqueous ethanol, CS₂ (2 mol equivalents), and KOH (2 mol equivalents) (86JOC2391).

The enantiometric purity of these new chiral heterocycles can be determined by high-performance liquid chromatography (HPLC) and NMR (¹H and ¹⁹F) analyses of their (*R*)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (MPA) amides.



The merits of asymmetric synthesis employing C4-chiral thiazolidines (**1**, **10**, and **11**) and oxazolidines (**2–5**) are as follows. (1) Commercially available α -amino acids and β -amino alcohols can be employed for the synthesis of C4-chiral heterocycles **1–5**, **10**, and **11**. (2) The almost-planar five-membered heterocyclic moiety clearly bisects the C4-chirality of the heterocycles. (3) The asymmetric induction should be analyzable by a UV detector attached to HPLC, because these heterocycles show a strong UV absorption

($\Pi \rightarrow \Pi^*$) with a high ϵ value. (4) Chiral nucleophilic reactions can be easily designed by utilizing an active amide structure of *N*-3-acylthiazolidine-2-thiones and oxazolidine-2-thiones (82H537).

III. Chiral Recognition in Aminolysis

A new *monitored aminolysis* of 3-acyl-1,3-thiazolidine-2-thione (ATT) has been developed by the authors (80TL841; 84CPB2687). This procedure has been applied to syntheses of several macrocyclic diamides (80CL159; 81H(15)1037), macrocyclic spermidine alkaloids (80TL4931; 81CC286), peptides (81CL463; 84JCS(P1)2439), and a spermidine siderophore, parabactin (84JCS(P1)183). The rate of the aminolysis was found to be remarkably affected by steric bulk of the amines. The end point of the reaction can easily be judged by disappearance of the original yellow color of ATT. A potential chiral recognition for racemic amines **15** by a chiral ATT derivative **14** was suggested by consideration of the foregoing aminolysis.

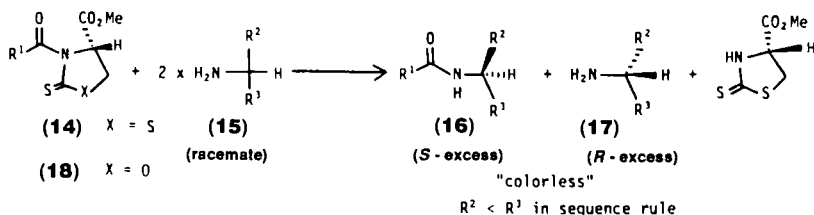
Thus, the mixture of a solution of *rac*-phenylglycine methyl ester in CH_2Cl_2 and a yellow solution of 3-hexadecanoyl-(4*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione (**14a**) in the same solvent was stirred at room temperature in nitrogen until the original yellow color of the medium vanished. A usual workup gave an optically active amide **16** in 93.7% yield [enantiomeric excess percent ($ee\%$) = 64.4 (*S* excess: $[\alpha]_D^{20} + 50.35^\circ$) based on the pure amide **16**] (82TL201). The *N*-acylation of (4*R*)-MCTT (**1**) was carried out by its treatment with hexadecanoyl chloride in the presence of Et_3N in tetrahydrofuran (THF) or by treatment of the thallium salt with hexadecanoyl chloride in THF.

The aqueous layer on usual workup gave optically active phenylglycine methyl ester hydrochloride in 83.4% yield [$ee\%$ = 45.9 (*R* excess: $[\alpha]_D^{20} - 60.59^\circ$) based on pure (*R*)-phenylglycine methyl ester hydrochloride: $[\alpha]_D^{20} - 132.13^\circ$] (Scheme 3).

Several other examples were summarized by Nagao *et al.* (82TL201). Thus a significant chiral recognition was realized in the aminolysis of 3-acyl-(4*R*)-methoxycarbonyl-1,3-thiazolidine-2-thiones [4(*R*)-AMCTT] (**14**) with racemic amines. In this reaction, (4*R*)-AMCTT (**14**) showed a preferential reactivity to the (*S*)-amine.

Comparison of the use of 3-acyl-(4*S*)-methoxycarbonyl-1,3-oxazolidine-2-thione [(4*S*)-AMCOT] (**18**) with that of (4*R*)-AMCTT (**14**) showed the superiority of the latter over the former.

The chiral recognition described above is available for the determination of the absolute configuration of a chiral amine. The method is as follows. *rac*-3-Hexadecanoyl-4-methoxycarbonyl-1,3-thiazolidine-2-thione (*rac*-



(14) a : $\text{R}^1 = (\text{CH}_2)_{14}\text{Me}$

b : $\text{R}^1 = \text{Ph}$

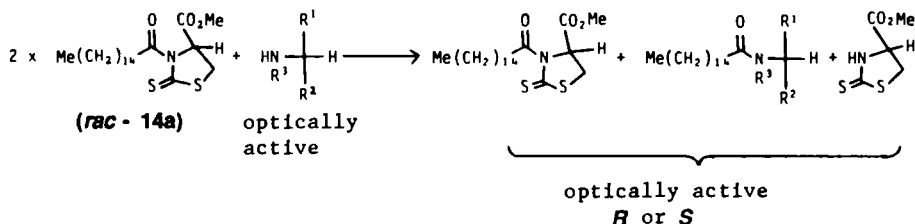
c : $\text{R}^1 = \text{CH}_2\text{Ph}$

d : $\text{R}^1 = 1\text{-adamantyl}$

SCHEME 3

HDMCTT) (*rac*-14a) (2 mol equiv) was subjected to aminolysis with 1 mol equiv of optically active amine (or imine). Then the specific rotation of the recovered HDMCTT (14a) was determined. By the sign of its specific rotation, the absolute configuration of the amine (or imine) can be assigned (82TL205).

Aminolyses of *rac*-14a were tried with several types of amines, i.e., α -amino acid derivatives, β -amino alcohols, and 3-amino- β -lactams (Scheme 4). The results are as follows. In the case of α -amino acid derivatives, the (*S*)-enantiomer reacted with (4*R*)-HDMCTT (14a) preferentially and vice versa [(*R*)-enantiomer + (4*S*)-HDMCTT], which was in good agreement with the chiral recognition of racemic amine with (4*R*)-AMCTT (14). In the case of β -amino alcohol derivatives, the (*S*)-enantiomer showed a preferential reactivity to (4*S*)-HDMCTT, resulting in the recovery of (4*R*)-HDMCTT. In the case of 3-amino- β -lactams, (*R*)-penam-, (*R*)-cephem-, and (*S*)-oxacephem derivatives all showed a preferential reactivity to (4*S*)-HDMCTT; (*R*)-oxacephem derivatives reacted predominantly with (4*R*)-HDMCTT.



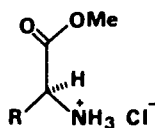
SCHEME 4

TABLE I
DETERMINATION OF ABSOLUTE CONFIGURATION

Chiral amino derivative	Preferred configuration (<i>R</i> or <i>S</i>) of the recovered HDMCTT	Absolute configuration of the optically active sample
α -Amino acid derivatives	<i>R</i> (-)	\longrightarrow <i>R</i>
	<i>S</i> (+)	\longrightarrow <i>S</i>
β -Amino alcohol derivatives	<i>R</i> (-)	\longrightarrow <i>S</i>
	<i>S</i> (+)	\longrightarrow <i>R</i>
3-Amino- β -lactam derivatives	Oxacephem and oxapenam	$\left\{ \begin{array}{l} R(-) \longrightarrow S \\ S(+) \longrightarrow R \end{array} \right.$
	Cephem and penam	$\left\{ \begin{array}{l} R(-) \longrightarrow R \\ S(+) \longrightarrow S \end{array} \right.$

On the basis of these results, the absolute configuration of chiral amines (or imines) can be determined, as summarized in Table I.

Apparent opposite chiral recognitions with **19** and **20** are attributed only to the (*R,S*) sequence rule by Cahn *et al.* (66AG(E)385).

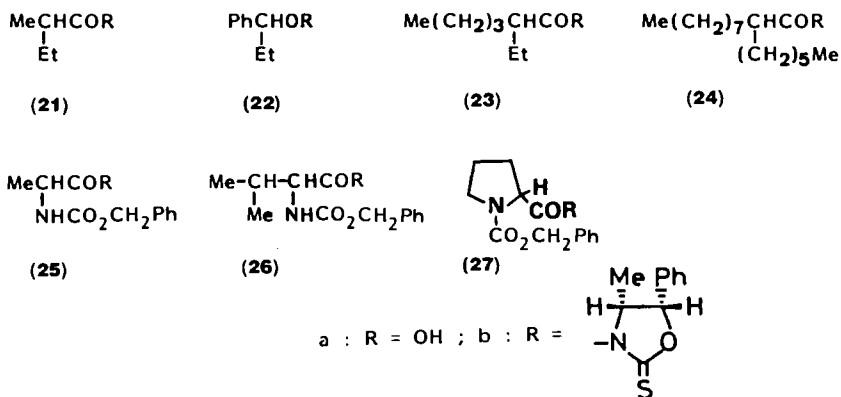


(19) $R = \text{CH}_2\text{SH}$

(20) $R = \text{CH}_2\text{SSCH}_2\text{CH}(\text{NH}_3^+\text{Cl}^-)\text{CO}_2\text{Me}$

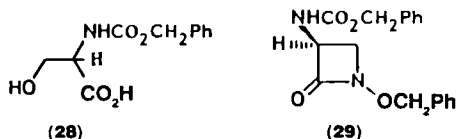
IV. Analytical Separation and Optical Resolution of Racemic Carboxylic Acids and Amino Acids

The determination of the enantiometric purity of optically active carboxylic acids and amino acids is important not only for an evaluation of their asymmetric syntheses, but optical resolution of racemic modifications of chiral carboxylic acid derivatives and chiral amino acids is also industrially important. A separation on both an analytical and a preparative scale of the racemically modified and commercially available carboxylic acids **21a–24a** and amino acids **25a–27a** was attempted by utilizing (4*R*,5*S*)-MPOT (**5**). The condensations between **5** and the carboxylic and amino acids **21a–27a** were carried out as usual to afford the corresponding 3-acyl-(4*R*,5*S*)-MPOT derivatives **21b–27b**. Their analytical separation was readily achieved by HPLC. ¹H-NMR techniques can also be useful for the analysis of the diastereoisomeric ratio of amides **21b–27b**.



The optical resolution of racemates **22a**, **25a**, and **27a** was carried out by chromatographic separation of their (4*R*,5*S*)-MPOT-amide derivatives **22b**, **25b**, and **27b**. The absolute stereochemistry of each pure diastereoisomer was confirmed by comparing the physical data of its derivative with those of the authentic compound in each case. Thus, (4*R*,5*S*)-MPOT (**5**) proved to be a satisfactory chiral reagent useful for analytical separation and optical resolution of racemic carboxylic acids and amino acids (85JCS(P1)2361).

This racemate separation method was applied to synthesis of the β -lactam **29** starting from the commercially available (*Z*)-DL-Ser-OH (**28**) (85JCS(P1)2361).

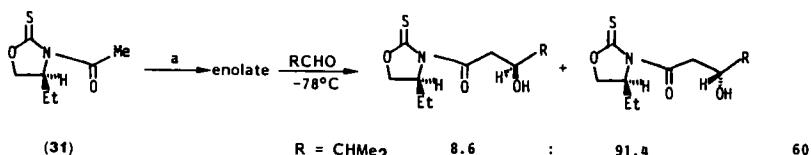
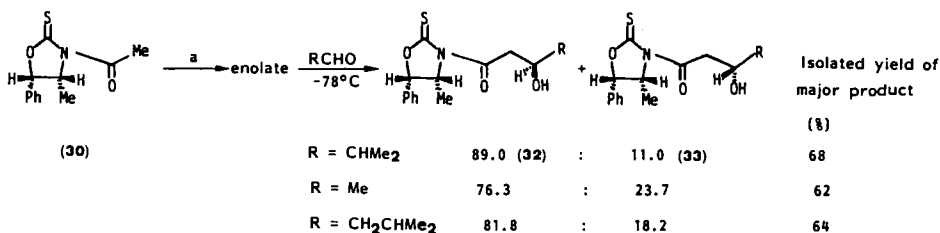


V. Highly Diastereoselective Aldol-Type Reactions

A. ALDEHYDES

1. Outline

A useful diastereoselective synthesis of aldols using chiral 3-acyl-1,3-oxazolidine-2-thiones **30**, **31**, **34**, and **35**, was developed. As described in Section II, (4*R*,5*S*)-MPOT (**5**) and (4*S*)-EOT (**2**) were prepared. These chiral heterocycles were employed as chiral auxiliaries. As enolating reagents, tin(II)



(a) Sn(O₃SCF₃)₂, *N*-ethylpiperidine, CH₂Cl₂
 -50 - -40 °C

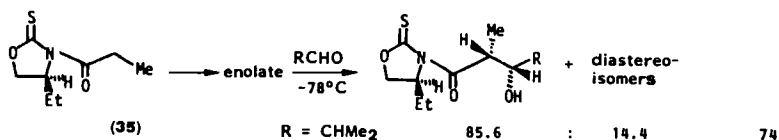
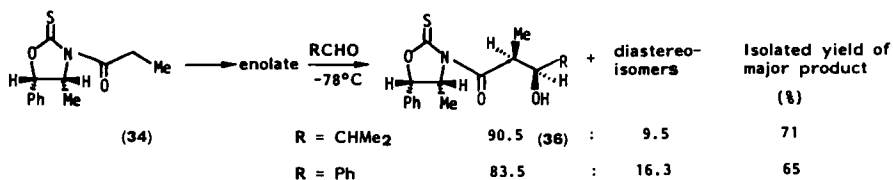
SCHEME 5

trifluoromethanesulfonate and *N*-ethylpiperidine were used according to Mukaiyama's procedure (83CL297).

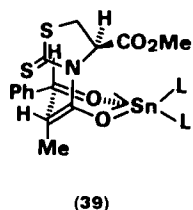
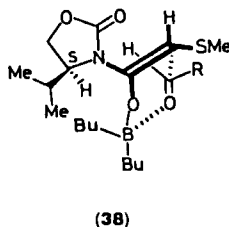
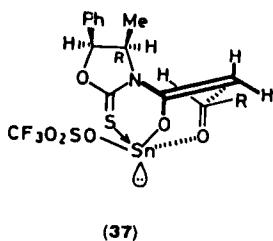
Thus, *N*-ethylpiperidine was added to a suspension of tin(II) trifluoromethanesulfonate in anhydrous CH₂Cl₂ at -50°C under Ar. After addition of a solution of 3-acetyl-(4*R*,5*S*)-MPOT (30) in CH₂Cl₂, the mixture was stirred at -50 to -40°C for 3 hr. A solution of isobutyraldehyde in CH₂Cl₂ was then added at -78°C and the mixture was stirred at the same temperature for 20 min. Usual workup of the reaction mixture gave a mixture of diastereoisomers 32 and 33, the ratio of which was readily checked by HPLC equipped with a UV detector. Chromatographic separation of each diastereoisomer gave optically pure 32 and 33 (Scheme 5).

Similar chiral aldol-type reactions using compound 30, 3-acetyl-(4*S*)-EOT (31), 3-propanoyl-(4*R*,5*S*)-MPOT (34), and 3-propanoyl-(4*S*)-EOT (35) gave fairly high diastereoselectivity (Schemes 5 and 6).

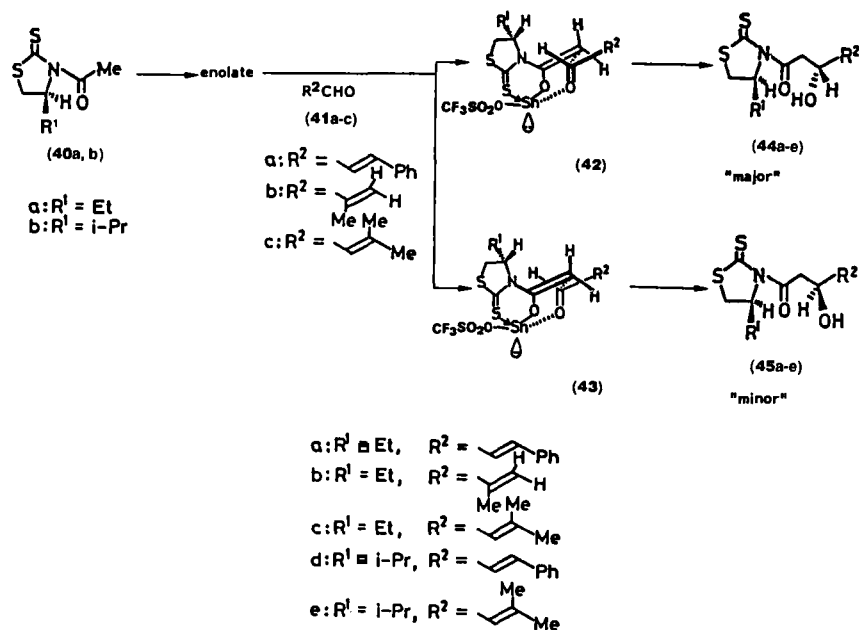
The stereochemical outcome shown in Schemes 5 and 6 can be rationalized in terms of an assumed transition state 37 (85CC1418). Interestingly, comparison of the transition state 37 involving tin(II) enolate with that in the Evans case (81PAC1109) (38) involving boron(III) enolate shows a remarkable contrast. It is also noteworthy that chiral recognition in the Miller case (87JOC2201) (39), employing (4*R*)-MCTT (1) and tin(II) trifluoromethanesulfonate, was just the opposite to ours.



SCHEME 6



A chiral synthon such as an α -nonsubstituted- β -hydroxy- γ,δ -unsaturated carbonyl compound should be useful for the synthesis of biologically active natural products, such as virginiamycins, compactin, nystatin A1, borrelidin, and leucomycins. In spite of its potential utility, no one has reported a chiral synthesis of any β -hydroxy- γ,δ -unsaturated carboxylic acid derivative by an aldol-type reaction because of its remarkable sensitivity toward base or acid under the reaction conditions. Asymmetric aldol-type reactions employing saturated aldehydes and acetyl derivatives have been reported by Evans (81JA2127), Mukaiyama (83CL297), and the authors (85CC1418). However, these reaction conditions cannot be used without improvement for chiral aldol-type reactions with α,β -unsaturated aldehydes. New C4-chiral 1,3-thiazolidine-2-thiones, (4*S*)-ETT (10) and (4*S*)-IPTT (11), were investigated as chiral auxiliaries. As the enolate-forming reagent, tin(II) trifluoromethanesulfonate and *N*-ethylpiperidine, the same system as described above, were used (Scheme 7). In this reaction, alcohols **44a-e** were afforded as major products in a highly diastereoselective manner (see Table II) (86JOC2391).



SCHEME 7

TABLE II
DIASTEREO-CONTROLLED ALDOL-TYPE REACTIONS BETWEEN
C4-CHIRAL 3-ACETYL-1,3-THIAZOLIDINE-2-THIONES (ATT)
AND α,β -UNSATURATED ALDEHYDES

ATT	Aldehyde	Diastereoisomer selectivity ^b	Isolated yield ^a (%)
40a	41a	92.7: 7.3 (44a:45a)	77.0
40a	41b	93.1: 6.9 (44b:45b)	74.2
40a	41c	88.6: 11.4 (44c:45c)	72.4
40a	41a	97.1: 2.9 (44d:45d)	81.2
40a	41c	97.3: 2.7 (44e:45e)	70.2

^a Total yield of both stereoisomers.

^b Determined by HPLC analysis (UV, 305 nm).

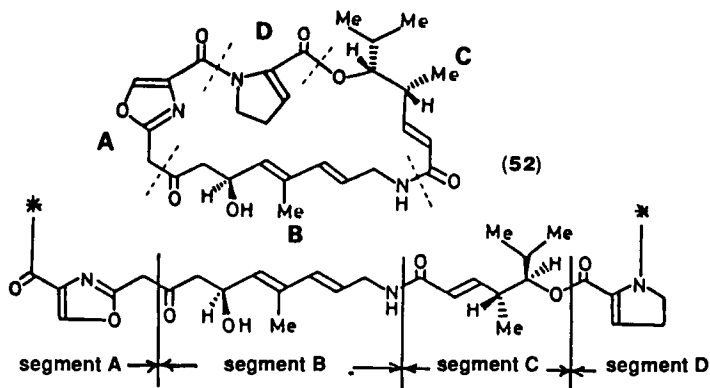
2. Synthetic Applications: Chiral Azetidinones and Virginiamycin M1

The aldol-type reaction described in Section V.A.1 was applied to the synthesis of chiral azetidinones **50** and **51** (Schemes 8 and 9).

Alcohol **46**, after protection with a *t*-butyldimethylsilyl (TBDMS) group to **47**, was converted into amide **48** by aminolysis with *O*-benzylhydroxylamine in CHCl_3 . The amide **48** was desilylated to give *N*-benzyloxy-(3*R*)-hydroxybutyramide (**49**), which was converted into 1-benzyloxy-(4*S*)-methyl-2-azetidinone (**50**), as shown in Scheme 8 (85CC1418).

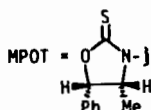
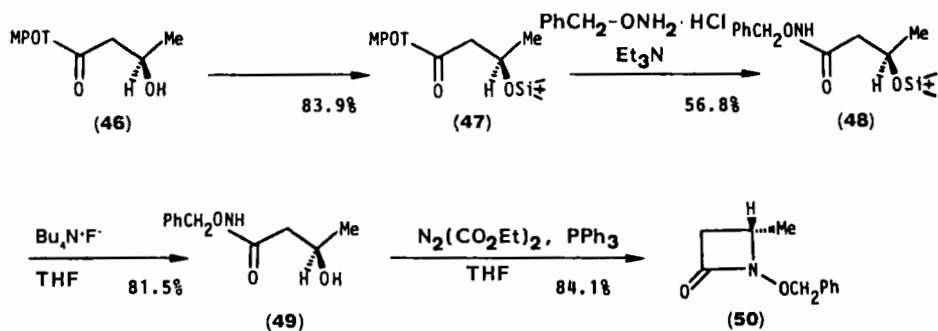
A chiral β -lactam (**51**) was also synthesized from **44c**, as shown in Scheme 9 (86JOC2391).

The second application of this method is concerned with the synthesis of virginiamycin M1 (**52**). Our synthetic strategy consisted of syntheses of four segments, A, B, C, and D, subsequent condensations between A and B and between C and D, followed by A-D condensation and final cyclization between B and C (83TL2287; 83TL2291).

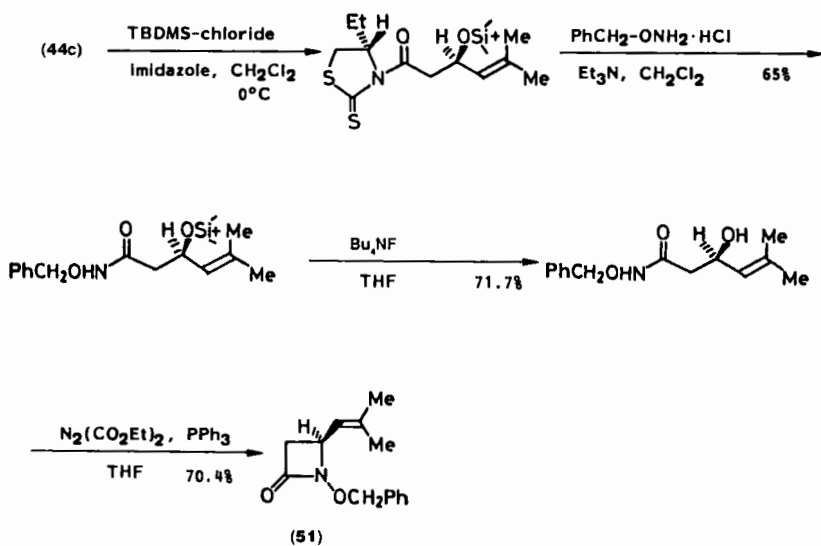


In the asymmetric syntheses of segments B and C, an aldol-type reaction is needed. Synthesis of segment C was carried out as follows. As mentioned, *N*-propanoyl-MPOT (**34**) was converted into **36** highly stereoselectively. After the secondary alcohol was protected as the tetrahydropyranyl (THP) ether, it was treated with diisobutylaluminum hydride (DIBAL) to give aldehyde **53**, which was subjected to a modified Wittig reaction (Wadsworth-Emmons modification) to give a trichloroethyl ester, **54**, of an α,β -unsaturated carboxylic acid. Deprotection gave finally segment C (**55**) (Scheme 10) (83UP1).

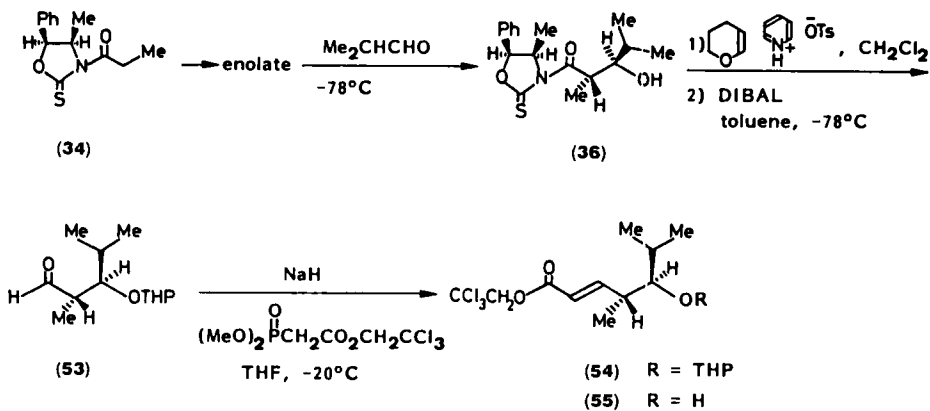
Segment B (**56**) in virginiamycin M1 was synthesized as shown in Scheme 11 (86UP1).



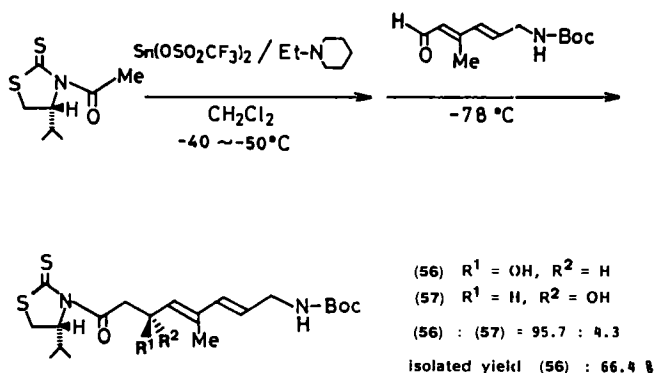
SCHEME 8



SCHEME 9



SCHEME 10



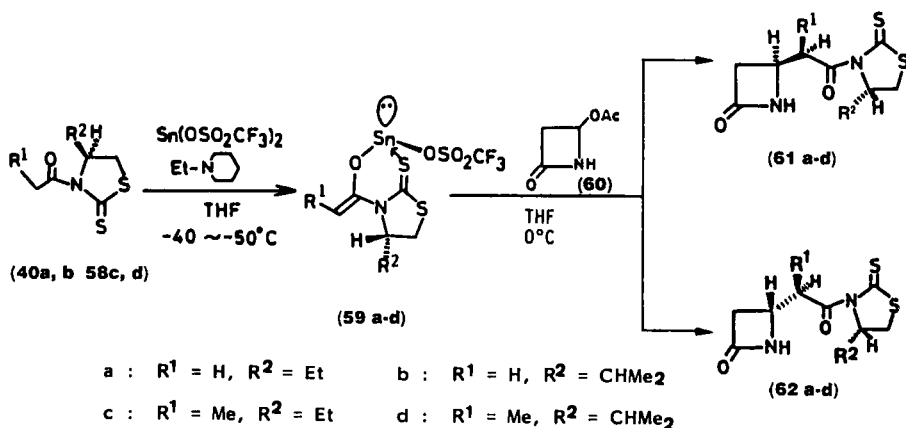
SCHEME 11

B. 4-ACETOXY-2-AZETIDINONES

1. Outline

A new efficient methodology for the preparation of a chiral 2-azetidinone intermediate applicable to the total synthesis of (+)-thienamycin and 1β -substituted carbapenems has been developed (86JA4673). This is based on the highly diastereoselective aldol-type reaction employing C4-chiral 3-acyl-1,3-thiazolidine-2-thiones and 4-acetoxy-2-azetidinones.

A THF solution of 4-acetoxy-2-azetidinone (60) at -40°C was added to tin(II) enolate 59a, which was prepared from 3-acetyl-(4S)-ethyl-1,3-thiazolidine-2-thione (40a). After stirring at 0°C for 1 hr, the reaction mixture

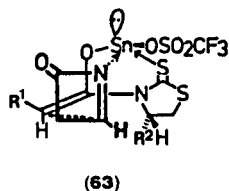


SCHEME 12

was subjected to the usual workup to afford a yellow mixture of **61a** and **62a** in a 95:5 ratio (HPLC analysis). The major product, **61a**, was readily isolated in 82% yield by silica gel column chromatography (Scheme 12). Other similar chiral alkylations of **60** by tin(II) enolates **59b-d** gave, with high diastereoselectivity in the range of 90:10–98:2 ratios, the corresponding 4-alkylated 2-azetidinones **61b-d** in 75–85% yields (Scheme 12).

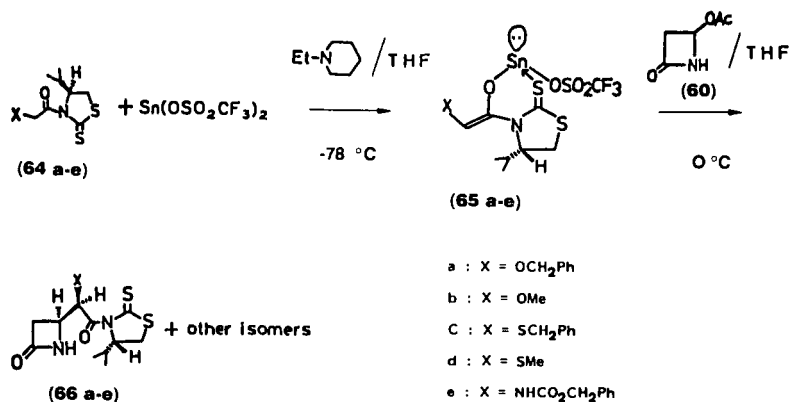
Stereochemistry of the major products **61a-d** was confirmed by the procedures of chemical conversion and X-ray analysis. The excellent *re* face selective alkylation into a presumed cyclic acylimine derived *in situ* from **60** was discussed and rationalized in terms of the most likely transition state, i.e., **63** (86JA4673).

Thus, the first aldol-type chiral alkylation of cyclic acylimine by tin(II) enolates of C4-chiral-1,3-thiazolidine-2-thiones was achieved.



A highly diastereo-controlled alkylation at the C4 position of **60**, employing chiral tin(II) enolates **65a-e** of heteroatom-substituted acetyl derivatives **64a-e**, provided **66a-e**, new synthetic intermediates for 1 β -heteroatom-substituted carbapenems (see Scheme 13 and Table III) (87CC602).

The absolute configuration of **66a** was established by its X-ray analysis. The stereochemistry of compounds **66b-e** was assigned from their 1H -NMR



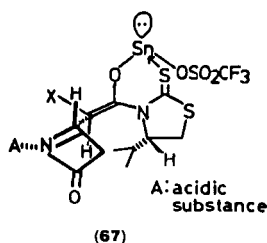
SCHEME 13

TABLE III
DIASTereo-CONTROLLED ALKYLATION OF
4-ACETOXY-2-AZETIDINONE (60) WITH
TIN(II) ENOLATES 65a-e

Tin(II) enolate	Diastereoisomer selectivity ^a (66: other isomers)	Isolated yield ^b (%)
65a	97:3	79 (66a)
65b	97:3	55 (66b)
65c	97:3	84 (66c)
65d	96:4	72 (66d)
65e	99:1	52 (66e)

^a Determined by HPLC analysis (UV, 305 nm).^b Based on 4-acetoxy-2-azetidinone (60).

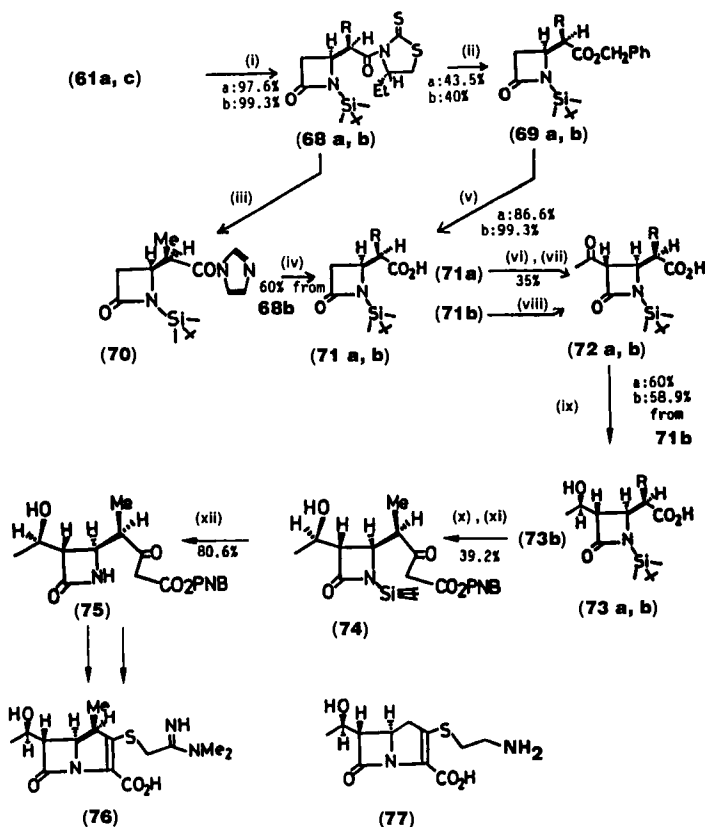
spectra and mechanistic considerations similar to those for 66a. The excellent stereochemical outcome for the major products 66a-e can be rationalized by postulating a six-membered chelating transition state like 63 or nonchelation transition 67.



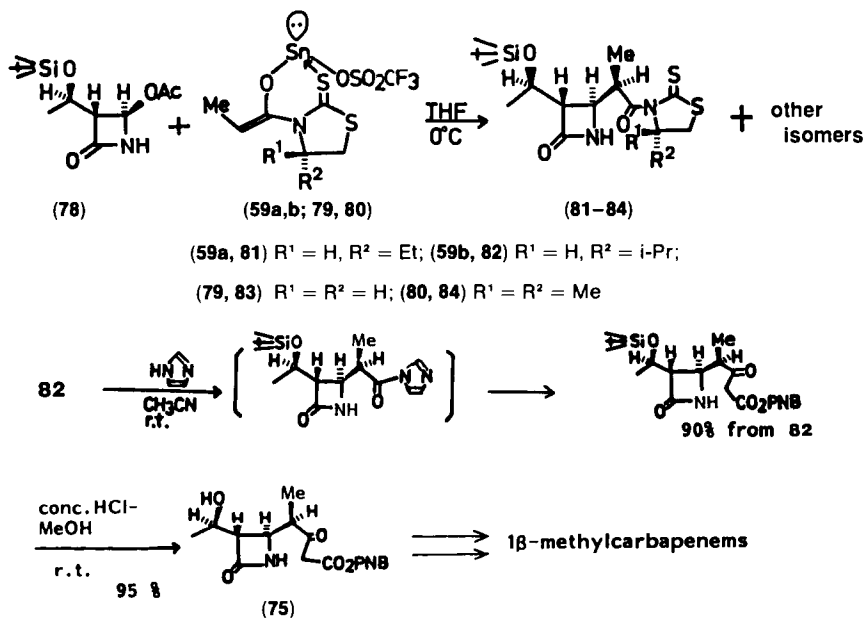
2. Synthetic Application: Carbapenems

Carbapenems are regarded as hopeful candidates for new-generation β -lactam antibiotics (78JA6491; 84H29). Thus, we applied our new chiral alkylation method to the synthesis of chiral β -substituted carbapenems and of the key intermediates for carbapenem syntheses.

C4-Alkylated azetidinones **61a** and **61c** were successfully converted to the new compounds **73a** and **73b**, as depicted in Scheme 14 (86JA4673). These compounds would be useful for the synthesis of (+)-thienamycin (**77**) or



SCHEME 14. (i) TBDMS-Cl, Et₃N, DMF, 0°C; (ii) PhCH₂ONa, toluene, 0°C (1 hr), r.t. (30 min); (iii) imidazole, THF; (iv) 1 N HCl, AcOEt; (v) H₂, 5% Pd-C, MeOH; (vi) LDA (2 eq), CH₃CHO, THF, -78°C; (vii) K₂Cr₂O₇, H₂SO₄, Et₂O-H₂O, -20°C; (viii) LDA (2 eq), THF, -40°C, N-acetylimidazole, THF, -78°C, r.t.; (ix) (i-Pr)₂NH · BH₃, (CF₃CO₂)₂Mg, Et₂O, -78°C; (x) carbonyldiimidazole, MeCN; (xi) Mg (O₂CCH₂CO₂PNB), 50°C; (xii) conc. HCl, MeOH. LDA, Lithium diisopropylamide; PNB, *p*-nitrobenzyl.



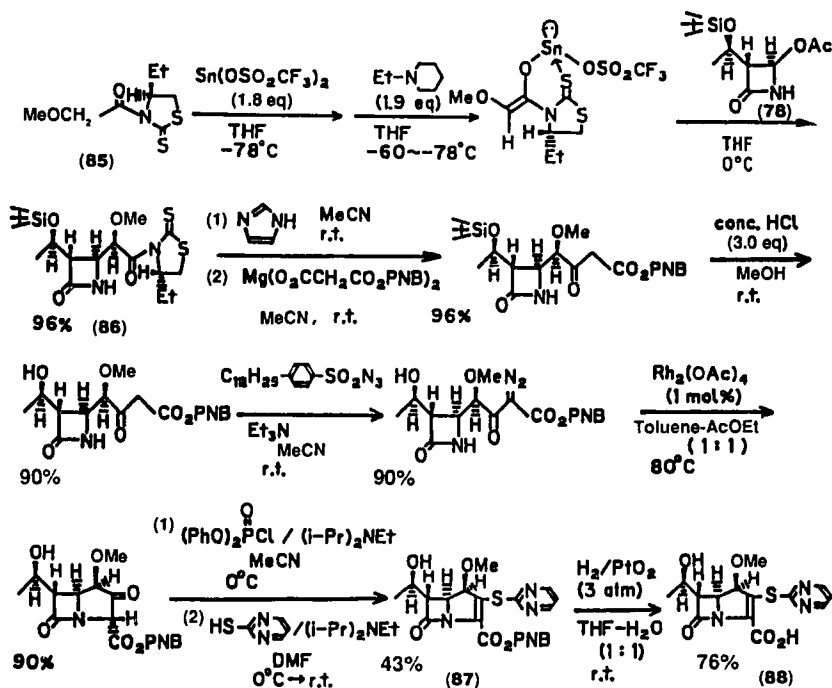
SCHEME 15

(-)-1β-methylcarbapenems (e.g., 76). In fact, compound 73b was transformed to the known key intermediate 75 (84H29), which had already been employed by Shih *et al.* for the synthesis of 76 (84H29).

Optically active 3-substituted 4-acetoxy-2-azetidinone (78) was similarly allowed to react with chiral tin(II) enolates 59a and b or achiral tin(II) enolates 79 and 80 in THF at 0°C for 1 hr to furnish the desired β-methyl products, 81 (80% yield) in a 90:10 (81/other isomers) ratio, 82 (74% yield) in a 91:9 ratio (82/other isomers), 83 in a 79:21 ratio (83/other isomers), and 84 in a 88:12 ratio (84/other isomers), respectively (Scheme 15) (86JA4673). Each minor product separated from a mixture with the corresponding β-(R)-methyl product was proved to be an α-(S)-methyl derivative, which was formed from the E-type tin(II) enolate of 3-propanoylthiazolidine-2-thiones.

Compound 82 was readily converted to the known key intermediate 75, which is useful for synthesis of 1β-methylcarbapenems (Scheme 15). Other alkylated azetidinones 81, 83, and 84 were also similarly converted to 75.

Alkylation of 78 with the tin(II) enolate of 3-methoxyacetyl-(4S)-ETT (85) gave β-methoxy derivative 86 in 96% yield and in a 98:2 ratio (86/other isomers). Major product 86 was subjected to sequential reactions depicted in Scheme 16 to afford a new 1β-methoxycarbapenem 88 (87UP1). The absolute stereochemistry of key intermediate 87 was confirmed by its X-ray analysis.



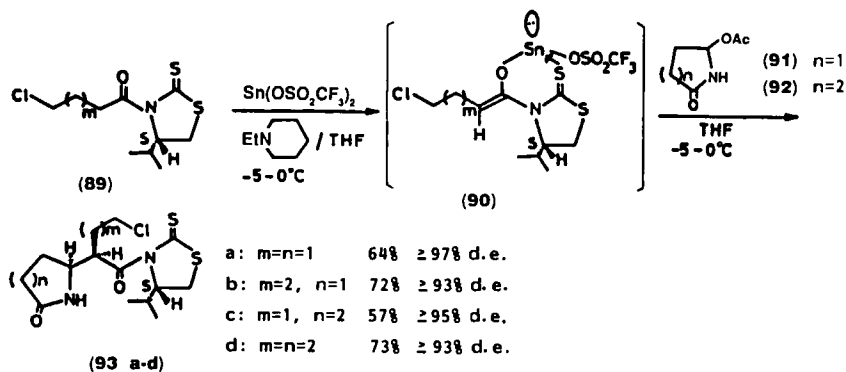
SCHEME 16

C. 5-ACETOXY-2-PYRROLIDINONE AND 6-ACETOXY-2-PIPERIDINONE

1. Outline

A new convenient procedure for the chiral alkylation of 5-acetoxy-2-pyrrolidinone (**91**) and 6-acetoxy-2-piperidinone (**92**) has been developed. This procedure should be useful for an extremely short chiral synthesis of the bicyclic alkaloids involving pyrrolizidine, indolizidine, and quinolizidine skeletons (88JA289).

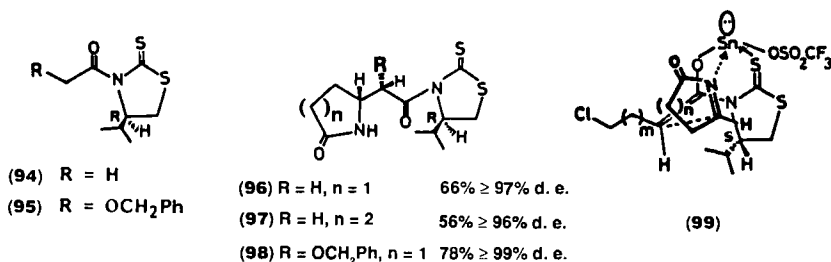
3-(ω -Chloroacyl)-(4*S*)-isopropyl-1,3-thiazolidine-2-thiones (**89**, $m = 1, 2$) were treated with a solution of tin(II) trifluoromethanesulfonate and *N*-ethylpiperidine in THF at -5 – 0°C for 3–4 hr to form the corresponding tin(II) enolates (**90**, $m = 1, 2$). Chiral alkylation of 5-acetoxy-2-pyrrolidinone (**91**) or 6-acetoxy-2-piperidinone (**92**) in THF at -5 – 0°C for 2 hr gave the corresponding major products **93a–d** in a highly diastereoselective manner [≥ 93 – 97% diastereomer excess (de)] and in 57– 73% yield (Scheme 17).



SCHEME 17

Similar chiral alkylations onto **91** and **92** using 3-acyl-(4*R*)-isopropyl-1,3-thiazolidine-2-thiones **94** and **95** were also carried out to give alkylated products **96–98** with high diastereoselectivities ($\geq 96–99\%$ de). The absolute stereochemistry of the major products **93a** and **d**, **96**, and **97** was established by their chemical conversions into known and related compounds.

Thus, highly diastereoselective alkylation with the chiral tin(II) enolates **90** can readily proceed regardless of the ring size of the cyclic acylimines prepared *in situ*. The stereochemical outcome can be rationalized by a unified six-membered transition state **99**. This can be supported by the experimental fact that the same chiral alkylation of *N*-1-methyl-5-acetoxy-2-pyrrolidinone with tin(II) enolate of 3-acetyl-(4*S*)-isopropyl-1,3-thiazolidine-2-thione (**40b**) gave a diastereomeric mixture of 5-alkylated products in 1:1 ratio.



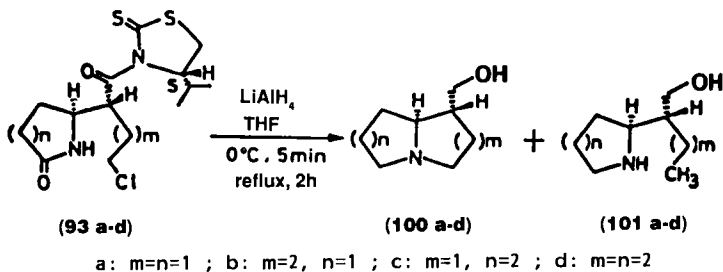
2. Synthetic Application: Bicyclic Alkaloids

There have been numerous papers related to the total synthesis of bicyclic alkaloids, such as pyrrolizidines, indolizidines, and quinolizidines, because of their interesting biological activities (e.g., anticancer activity).

However, there has been no report on the highly stereoselective chiral synthesis of (–)-trachelanthamidine (**100a**) and (+)-epilupinine (*ent*-**100d**) type alkaloids without the use of a chiral building block, except for Takano's chiral synthesis (33% optical purity) (81H(16)915).

We reported a new general method for an extremely short chiral synthesis of the bicyclic alkaloids having a nitrogen atom ring juncture utilizing a highly diastereoselective alkylation to the cyclic acylimines, followed by reductive annulation of the resultant cyclic imines (88JA289).

Thus, a one-pot and one-reagent (LiAlH_4) synthesis of the chiral bicyclic alkaloids **100** from **93** was designed. ω -Halolactams **93a–d** were treated with LiAlH_4 (4 mol equiv) in THF; first at 0°C for 5 min to reduce the active amide moiety without epimerization at the asymmetric methine carbon and then at reflux for 2 hr to achieve reductive cyclization. After the usual treatment of the reaction medium, the desired bicyclic products **100a–d** (41–69% yield) were obtained directly together with the corresponding hydrogenated by-products **101a–d** (Scheme 18 and Table IV). Cyclization products **100a–d**



SCHEME 18

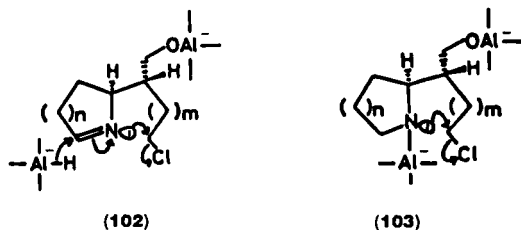
TABLE IV
REDUCTIVE CYCLIZATION OF COMPOUNDS **93a–d**^a

Substrate	Product (yield)	By-product (yield)	Ratio of 100 : 101
93a	100a (44%)	101a (10%)	4.4:1
93b	100b (41%)	101b (22%)	1.9:1
93c	100c (69%)	101c (trace)	∞
93d	100d (61%) ^b	101d (18%)	3.4:1

^a The auxiliary (4S)-IPTT was recovered in 70–90% yield in all cases.

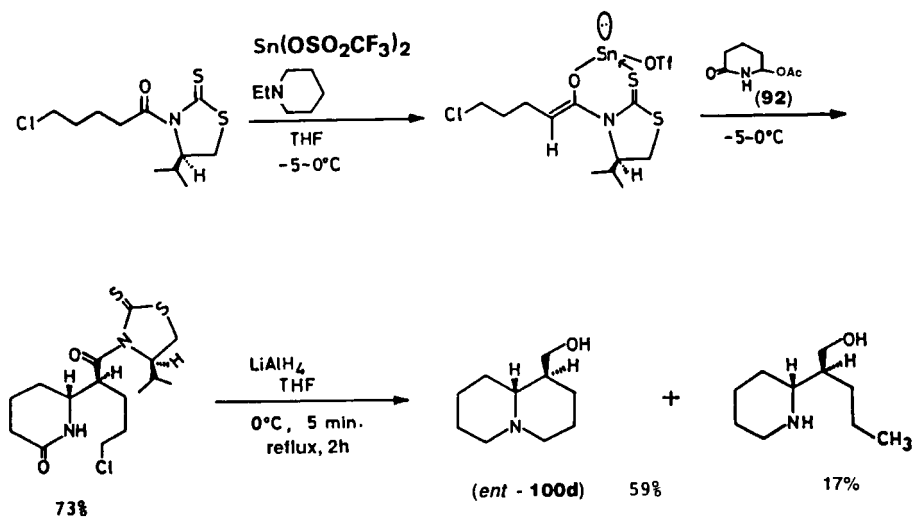
^b Colorless needles (mp, 76–76.5°C) from hexane.

may be formed *via* the presumed transition state **102** (concerted) and/or **103** (stepwise).



Compound **100a** (99% optically pure) proved to be (–)-trachelanthamidine by comparison of its physical data with those of the naturally occurring compound (63CJC1919; 84JOC1682). Since compound **100d** was determined to be (–)-epilupinine in a similar manner, naturally occurring (+)-epilupinine (*ent*-**100d**) (51NZJ(B)50; 84JOC1682) was also synthesized according to the simple procedure shown in Scheme 19.

New empirical conclusions for the reductive cyclization toward the *N*-atom-containing bicyclic compounds may be presented based on the results shown in Table IV. Namely, five-membered annulation toward the 6–5-type bicyclic ring system exhibits the best reactivity among all bicyclic ring



SCHEME 19

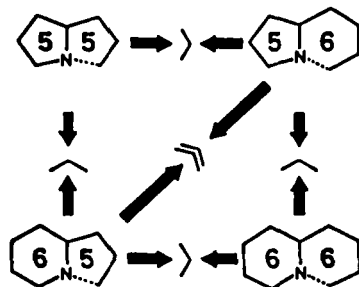


FIG. 1. Reaction order for the reductive annulation.

formations. Conversely, six-membered annulation toward the 5-6-type bicyclic ring system is the least reactive (Fig. 1).

VI. Highly Selective Nonenzymatic Chiral Induction onto Prochiral σ -Symmetric Dicarboxylic Acids

Highly enantioselective differentiation between two identical ligands in prochiral σ -symmetric dicarboxylic acid esters had been exclusively performed only by utilizing microorganisms or enzymes, such as α -chymotrypsin, pig liver esterase, and pig pancreatic lipase (84PM11) before our chemical success (82JA2079). Although some nonenzymatic methods (54PNA499; 56JA5091) for chiral induction into phenylglutaric anhydride were reported before our case, they were unsatisfactory from the viewpoint of diastereoselectivity.

We developed a novel method for a highly stereoselective differentiation between two identical groups in prochiral σ -symmetric dicarboxylic acids based on a completely new idea employing (4*R*)-MCTT (**1**). The dipole-dipole repulsion between the carbonyl and the thiocarbonyl groups in the (4*R*)-MCTT amide system was utilized in order to regulate the free rotatory molecule in the transition state for chiral induction (see Fig. 2).

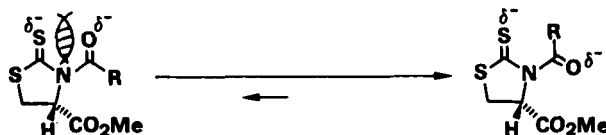
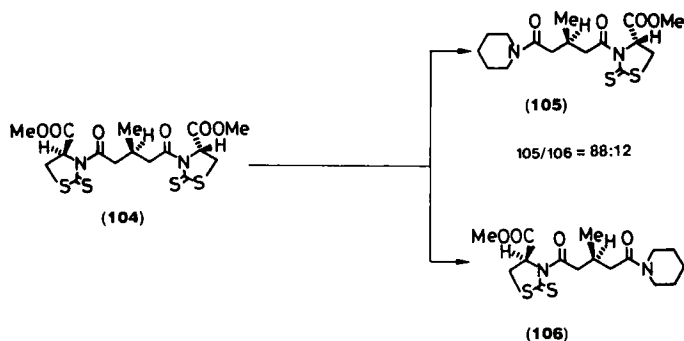


FIG. 2. Dipole-dipole repulsion between carbonyl and thiocarbonyl groups.



SCHEME 20

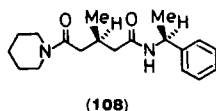
A. 3-METHYLGLUTARIC ACID

Attempts were made to develop a new chiral design based on the symmetry of organic molecules without using metal chelation.

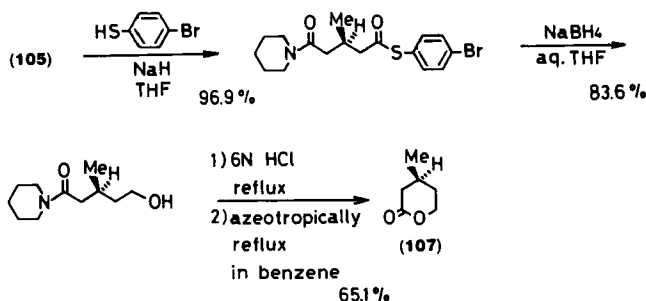
The important key compound **104**, a diamide of 3-methylglutaric acid and (4*R*)-MCTT (**1**), was designed by considering the transition state in its reaction with a nucleophile. Its crystallographic structure was shown to have a conformation supporting, in principle, our working hypothesis (82JA2079; 85JOC4072).

Compound **104** was subjected to aminolysis with 1 mol equiv of piperidine, the most useful amine nucleophile in the preliminary test, in CH_2Cl_2 at -30°C . As the result, a pure major product **105** as yellow needles and a pure minor product **106** as a yellow oil were obtained in a ratio of 88:12 (Scheme 20).

The absolute configuration of **105** was established by its chemical conversion (Scheme 21) into the known lactone **107** (77JA556) and by X-ray analysis of amide **108**, which was derived from **105**. The stereochemistry of **106** was confirmed by its chemical conversion into the antipodal compound of **108**.



The major product **105** was subjected to reactions with several nucleophiles to afford the corresponding optically pure compounds in high yield. Thus, the first highly selective nonenzymatic chiral induction was achieved using 3-methylglutaric acid.



B. *meso*-2,4-DIMETHYLGLUTARIC ACID

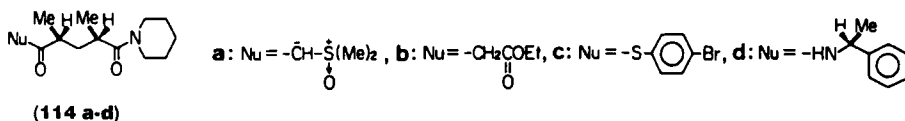
1. Outline

The highly enantioselective transformation of dimethyl *meso*-2,4-dimethylglutarate into its half ester had been performed only by a microorganism, *Gliocraudium roseum* (81JA3580), and no report of a chemical chiral induction had been published before our success.

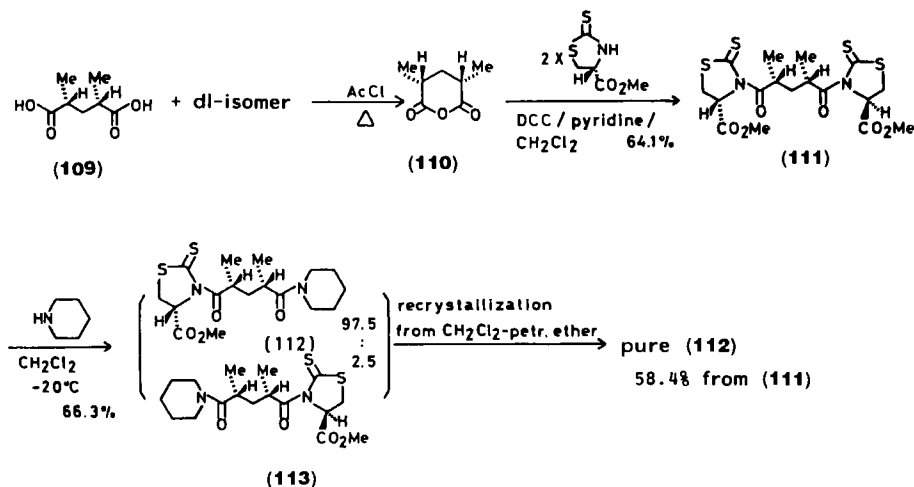
An extremely regioselective high differentiation between two identical groups in *meso*-2,4-dimethylglutaric acid (**109**) has been achieved (83JOC132; 84T1215).

meso-2,4-Dimethylglutaric anhydride (**110**) was converted to (4*R*)-MCTT-diamide **111**, which on aminolysis with piperidine gave a solid mixture of **112** and **113** in a ratio of 97.5:2.5. Pure compound **112** was easily obtained (Scheme 22). The pure compound **113** was prepared in sufficient quantity by treatment of **111** with 2 mol equiv of piperidine (to yield a 1:1 mixture of monopiperidineamides), then with 1 mol equiv of (4*R*)-MCTT (**1**). The absolute stereochemistry of **112** and **113** was clarified by their X-ray analysis.

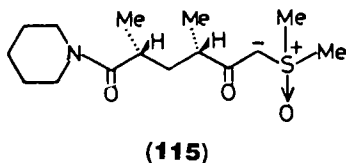
The second reactions of compound **112** with several nucleophiles gave enantiomeric pure products **114**.



Compound **113** was converted to **115**, which was confirmed to be an enantiomer of **114a** derived from **112**.

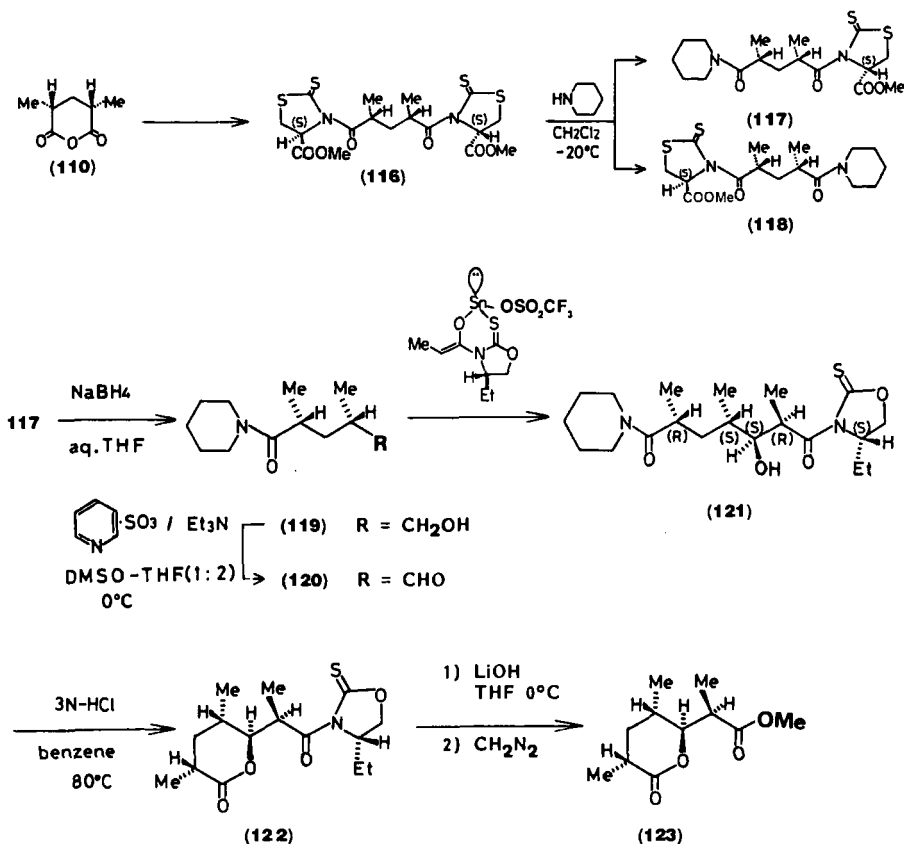


SCHEME 22



2. Synthetic Application: (+)-Prelog-Djerassi Lactonic Acid Methyl Ester

The method described in Section VI,B,1 was useful for the short synthesis of the Prelog-Djerassi lactonic acid methyl ester, a key intermediate for the synthesis of macrolides and polyether antibiotics. Thus, *meso*-2,4-dimethylglutaric anhydride (**110**) was converted to (4*S*)-MCTT-diamide **116**, which on aminolysis with piperidine gave a mixture of **117** and **118** in a ratio of 97.3:2.7. Pure compound **117**, easily obtained, was converted into aldehyde **120** via alcohol **119**. Compound **35** was enolated as described above, and the resulting enolate was subjected to an aldol-type reaction with aldehyde **120** to afford (*S*)-alcohol **121** with a high diastereoselectivity. Treatment of **121** with acid gave lactone **122**, which on treatment with base followed by methylation finally gave (+)-Prelog-Djerassi lactonic acid methyl ester **123** (Scheme 23) (81JOC479; 85CC1419).



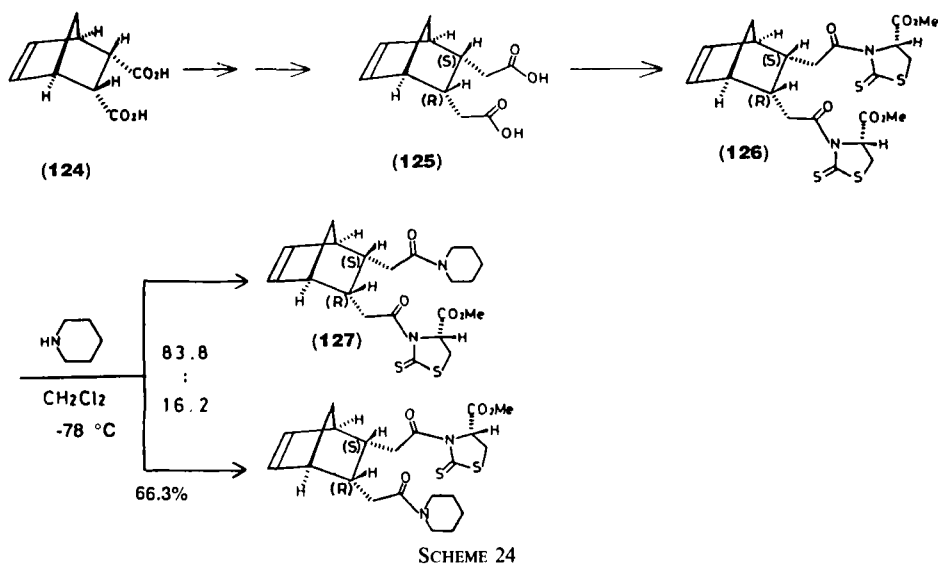
SCHEME 23

C. *meso*-5-NORBORNEN-2,3-YLENE-endo-BIS(ACETIC ACID)

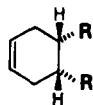
meso-5-Norbornen-2,3-ylene-endo-bis(acetic acid) (**125**) was derived from commercially available *meso*-5-norbornen-2,3-ylene-endo-bis(formic acid) (**124**). The (4*R*)-MCTT-diamide (**126**) was subjected to aminolysis with 1 mol equiv of piperidine to give **127** with a high selectivity (Scheme 24) (84T1215).

D. *cis*-4-CYCLOHEXEN-1,2-YLENEBIS(ACETIC ACID)

Highly enantioselective chiral induction into conformational enantiomers such as diol **128** (82JA4659) and dimethyl ester **129** (84AG140; 84AG(E)67; 84TL2557) has been carried out via the enzymatic procedure. However, chemical chiral induction into conformational enantiomers had never been published before our example.



SCHEME 24

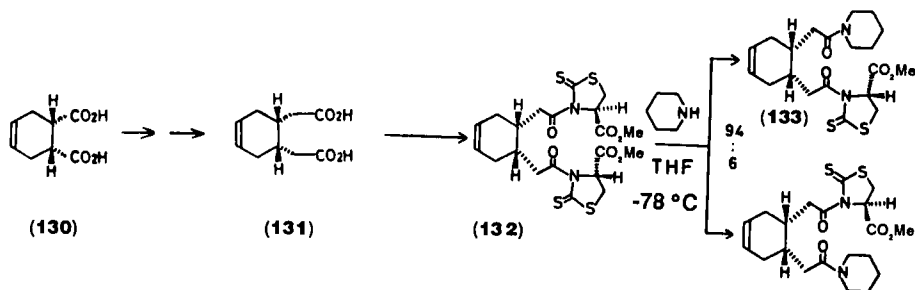
(128) $\text{R} = \text{CH}_2\text{OH}$ (129) $\text{R} = \text{CO}_2\text{Me}$

1. Outline

cis-4-Cyclohexen-1,2-ylenebis(acetic acid) (**131**) was derived from a commercially available *cis*-4-cyclohexen-1,2-ylenebis(formic acid) (**130**). The (4*R*)-MCTT-diamide (**132**) was subjected to aminolysis with 1 mol equiv of piperidine to give **133** with a high selectivity (Scheme 25) (85JOC4072).

2. Synthetic Application: (+)-Carbacyclin

(+)-Carbacyclin (carba- PGI_2) (**146**) is a stable analog having a physiological activity similar to that of prostacyclin (PGI_2) (78CC1067, 78TL1371). Since its discovery, numerous syntheses of **146** have been reported by utilizing the optically active Corey lactone and its related compounds (79CL1437, 79JOC2880, 79TL433, 79TL2607; 80JOC4776; 81AG(E)1046, 81JOC1954, 81T4391; 84AG(E)142, 84CPB2886). We succeeded in a new chiral synthesis of (+)-carbacyclin (**146**) according to our chiral induction design (87CC267).

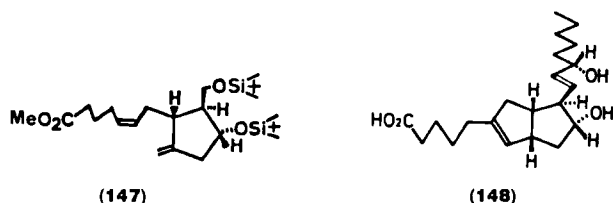


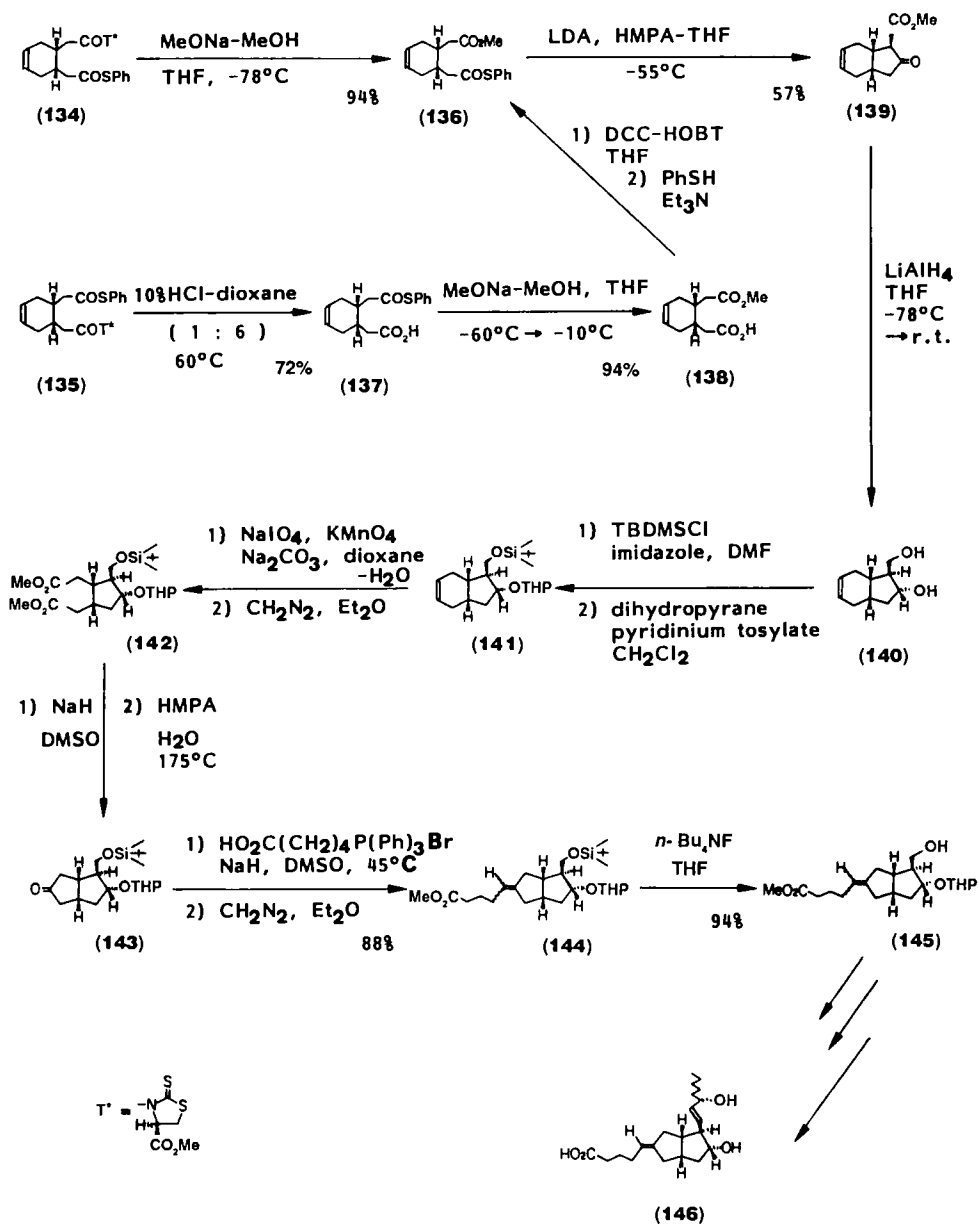
SCHEME 25

By using various nucleophiles [PhSLi , PhSNa , PhSH-DBU ($\text{DBU} = 1,8\text{-diazabicyclo}[5,4,0]\text{undec-7-ene}$), $\text{PhSH-Et}_3\text{N}$, $t\text{-BuSLi}$, PhOLi , MeOH-Lewis acid], further similar differentiation reactions between two identical groups in $(4R)\text{-MCTT-diamide } 132$ were examined. In view of diastereoselectivity, yield, and chromatographic separation of two diastereomeric products, thiolysis of **132** with PhSH in the presence of Et_3N was adopted. From the resulting products, the pure major product **134** was separated from the minor product **135**. The major product **134** was converted to a half-thiol diester **136** by the selective methanolysis with MeONa . The minor product **135** was converted into **136** via **137** and **138**. Dieckmann cyclization (87CL1861) of **136** afforded a β -keto ester **139**, which, after reduction with LiAlH_4 to diol **140**, on selective protection gave a doubly protected diol **141**. Lemieux-Rudloff oxidation of **141**, followed by esterification, gave diester **142**. Ring closure with dimsyl sodium followed by demethoxycarbonylation converted **142** into bicyclic pentanone **143**, whose Wittig reaction and subsequent selective deprotection of the TBDMS group yielded a mixture of olefinic products **145** and **144**. The conversion of **145** to $(+)\text{-carbacyclin (146)}$ was achieved by the known procedure developed by the Ono research group (81T4391) (Scheme 26).

$(+)\text{-Isocarbacyn (148)}$ also exhibited fairly powerful inhibition of platelet aggregation (83TL3493). Therefore, chiral synthesis of a useful intermediate **147** (84TL1067) for $(+)\text{-isocarbacyn (148)}$ was tried with success (87CC269).

In this synthesis, compound **140** was used as the starting material.

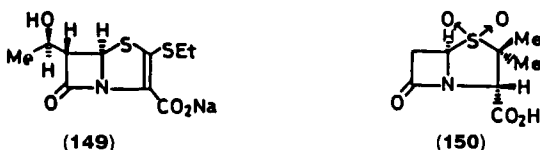




SCHEME 26. HMPA, Hexamethylphosphoramide; HOBT, 1-hydroxybenzotriazole.

VII. Methylseleno-Promoted Ketene-Imine Cycloaddition Reaction

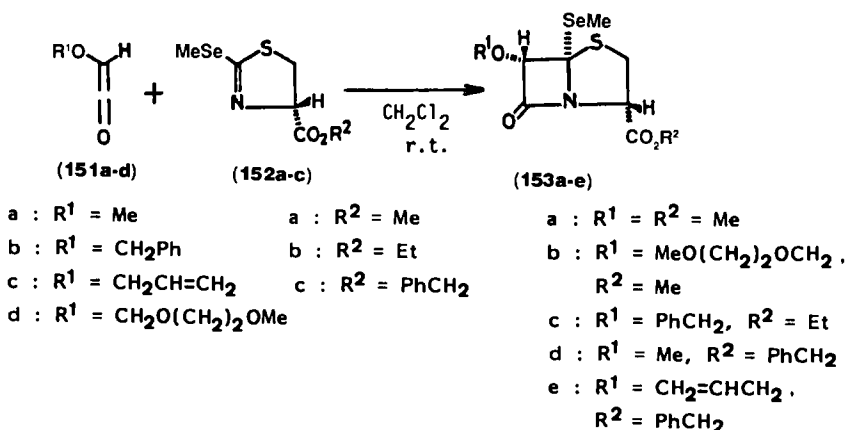
A synthetic penem-type β -lactam (**149**) exhibited antibacterial activities similar to (+)-thienamycin (**77**) (82JA6138). Sulbactam (**150**) showed fairly strong inhibitory activity against β -lactamase (78AAC414). Based on the background mentioned above, we developed a new convenient method for the synthesis of penam-type β -lactams.



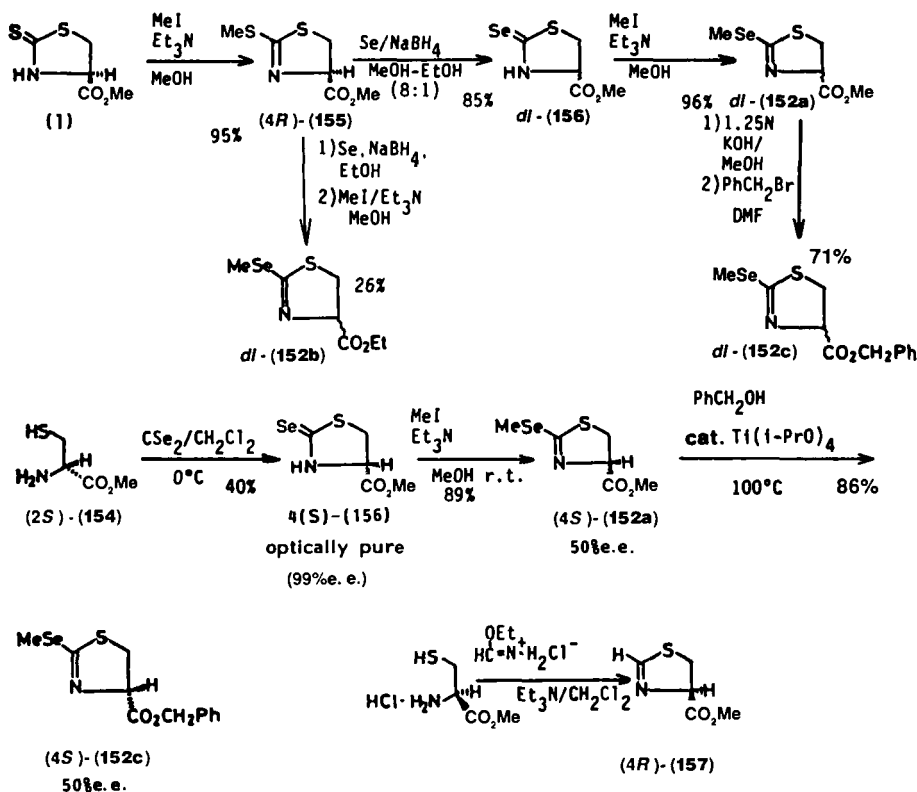
In 1977, Bose and co-workers (77JCS(P1)1117) reported a synthesis of penams with a methylthio substituent on the ring junction carbon atom by condensation of cyclic methylthioimide and acetyl chloride under basic conditions. However, selective demethylsulfurization at the ring juncture of the bicyclic penams is difficult. Hence, this method is of limited utility.

A new methylseleno-promoted ketene-imine cycloaddition reaction between **151** and **152** (86JOC4737) gave the bicyclic product **153** in an extremely high stereoselective fashion and in fairly good yield (36–92%) (Scheme 27).

New cyclic methylseleno imino compounds were synthesized from (4*R*)-MCTT (**1**) or D-cysteine methyl ester (**154**) (Scheme 28) (86JOC4737).



SCHEME 27

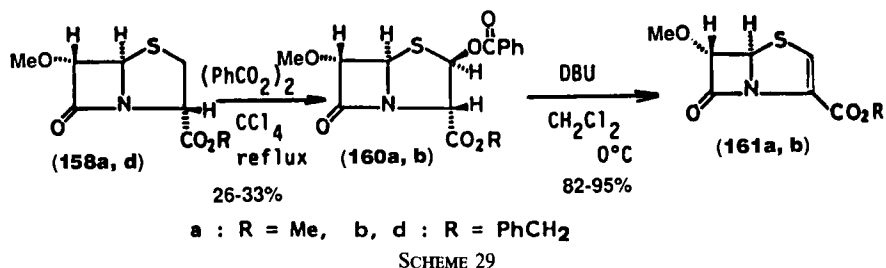


SCHEME 28

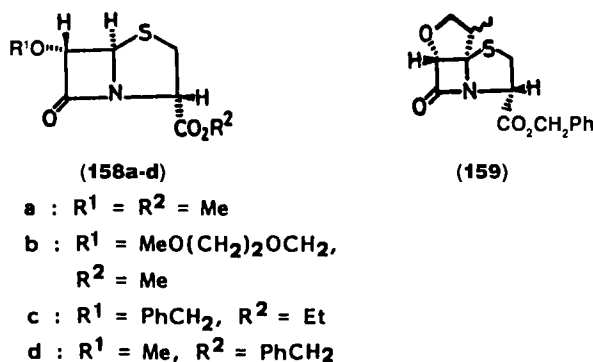
The reaction between methoxyacetyl chloride and (4R)-155 or (4R)-157 gave the corresponding bicyclic product in a moderate yield [58% in (4R)-155] or in a very poor yield [5% in (4R)-157] (compared to the 81% yield of 153a). Thus, a methylseleno substituent on the imine moiety promoted this ketene–imine cycloaddition reaction.

Reductive demethylselenation of 153a–d with *n*-Bu₃SnH in refluxing THF and CH₃CN or in CH₃CN at 60°C in the presence of catalytic 2,2'-azabisobutyronitrile (AIBN) gave 158a–d with a high stereoselectivity and in good yield (56–83%). Similar demethylselenation of dl-153e gave tricyclic products dl-159 (62% yield), a mixture of diastereoisomers due to a secondary methyl group.

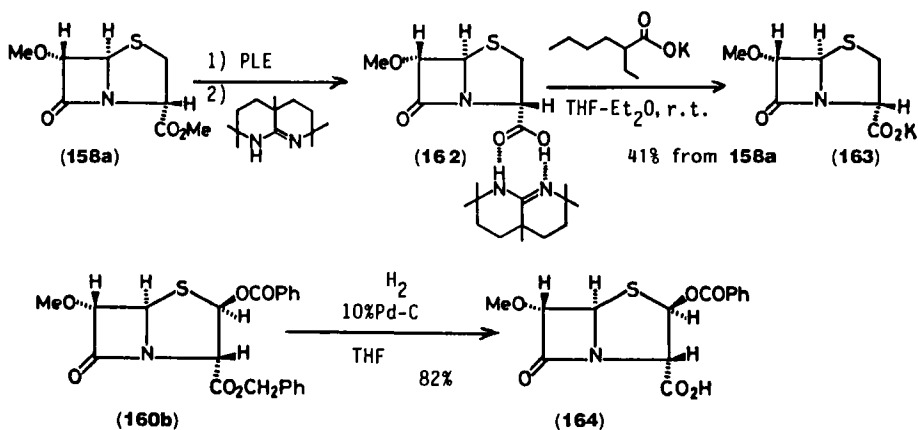
Penams 158a and d were treated with benzoyl peroxide (4 mol equiv) in refluxing CCl₄ to give the corresponding benzoyloxy derivatives 160a and b, which were converted to penems 161a and b in high yield in the presence of DBU (Scheme 29).



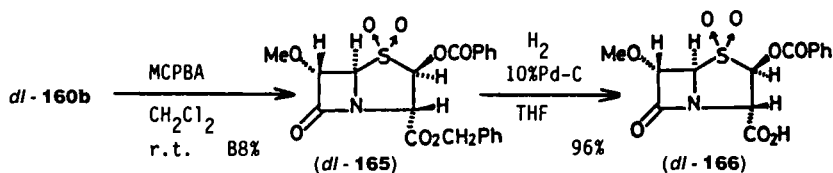
SCHEME 29



Enzymatic hydrolysis of penam **158a** with porcine liver esterase (PLE) followed by treatment with Eschenmoser's base (78HCA2851; 82T2659) afforded salt **162**, which was treated with potassium 2-ethylhexanoate in



SCHEME 30



SCHEME 31

THF-Et₂O to give the potassium salt **163** of penam carboxylic acid (Scheme 30) (87NKK1447). Hydrogenolysis of the benzyloxycarbonyl group of **160b** gave penam carboxylic acid **164** in 82% yield (87NKK1447).

In order to obtain a sulbactam-like compound, *dl*-**160b** was oxidized with *m*-chloroperbenzoic acid (MCPBA) (2 mol equiv) to give *dl*-**165**, which was subjected to the usual hydrogenolysis method giving penam carboxylic acid 1,1-dioxide (*dl*-**166**) in excellent overall yield (87NKK1447) (Scheme 31).

VIII. Conclusion

The C4-chiral thiazolidine-2-thiones and oxazolidine-2-thiones developed by us proved to be efficient for chiral induction. They should be applicable to practical syntheses of drugs. Novel chiral designs using these functional and chiral heterocycles seem likely in the future, especially when used in combination with organometallic reagents and/or molecular symmetry. Creative investigations employing such chiral heterocycles and related compounds will be extensively pursued.

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Heterocyclic Quinones

MIHA TIŠLER

*Department of Chemistry and Chemical Technology,
Edvard Kardelj University,
61000 Ljubljana, Yugoslavia*

I. Introduction	38
II. Quinones with a Condensed Four-Membered Heterocyclic Ring.	39
III. Quinones with a Condensed Five-Membered Ring with One Heteroatom	39
A. Pyrrole Derivatives	39
Isoindole Derivatives	53
B. Furan Derivatives	54
1. Tricyclic Systems.	56
2. Tetracyclic Systems	63
3. Pentacyclic and Higher Systems	65
4. Isobenzofuran Derivatives	67
C. Thiophene Derivatives	69
IV. Quinones with a Condensed Five-Membered Ring with Two Heteroatoms	74
A. Pyrazole Derivatives	74
B. Isoxazole and Isothiazole Derivatives.	77
C. Imidazole Derivatives	79
D. Oxazole and Thiazole Derivatives	80
E. 1,3-Dioxolane and 1,3-Dithiolane Derivatives	81
V. Quinones with a Condensed Five-Membered Ring with Three Heteroatoms.	82
A. Triazole Derivatives.	82
B. Thiadiazole Derivatives	83
VI. Quinones with a Condensed Six-Membered Ring	84
A. Azaquinones	84
B. Quinoline Derivatives	85
C. Streptonigrin and Lavendamycin	88
D. Extended Systems	90
E. Isoquinoline Derivatives	92
F. Pyridazine Derivatives	97
G. Pyrimidine Derivatives.	98
H. Pyrazine Derivatives	99
I. Pyran Derivatives	100
1. Chroman- and Isochromandiones	100
2. Tricyclic Systems.	102
a. Derivatives of Naphtho[2,3- <i>b</i>]pyran-5,10-dione and Naphtho[1,2- <i>b</i>]pyran-5,6-dione	102
b. Derivatives of Naphtho[2,3- <i>c</i>]pyran-5,10-dione, Tetracyclic, and Higher Systems	105
J. Derivatives of 1,4-Dioxane, 1,4-Dithiane, and 1,4-Oxathiane.	114
1. 1,4-Dioxane Derivatives	114
2. 1,4-Dithiane Derivatives	115
3. 1,4-Oxathiane Derivatives.	115

K. Derivatives of 1,4-Oxazine and 1,4-Thiazine	116
1. 1,4-Oxazine Derivatives	116
2. 1,4-Thiazine Derivatives	117
VII. Quinones with Two Different Heterocyclic Systems	
Attached to the Quinone Moiety.	118
A. Pyrroloquinolinequinones.	118
B. Other Systems.	119
VIII. Miscellaneous Heterocyclic Quinones	121
IX. Appendix.	122
References	124

I. Introduction

The quinone moiety is found commonly in nature. Quinones, including heterocyclic analogs, are involved in numerous biochemical processes because of their facile reduction–oxidation. They play an important role in electron transport processes and oxidative phosphorylation processes. Furthermore, their biological activity includes enzyme inhibition and some have chemotherapeutic value as antitumor, antibacterial, antifungal, and anticancer agents.

In this article, the chemistry of heterocyclic quinones is presented. Only those heterocyclic quinones that have a heterocyclic ring attached directly to the quinone moiety are included. To date, heterocyclic quinones have been partially reviewed, together with naturally occurring quinones (71MI1), as potential precursors to quinoneimides (86MI1), together with the quinone mono- and diimides (87MI1), and with 1,2- and 1,4-quinones (69QR204; 77HOU; 79HOU). Voluminous research on quinones, including some heterocyclic ones, was done by Samuel C. Hooker and the work was published in part at the end of the last century. After Hooker's death, Louis F. Fieser completed and published his results in 11 papers in 1936 in the *Journal of the American Chemical Society*. The chemistry of polyheterocyclic quinones obtained from 2,3-dihalo-1,4-naphthoquinones has been reviewed to the year 1962 (62CRV279). Reviews on some biologically important quinones, such as mitomycins (79MI1, 79MI2; 87MI2) and streptonigrin (77H1485; 82MI1) have appeared.

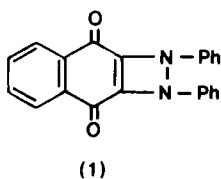
Biological activity of some quinoline-5,8-diones, quinoxalin-5,8-diones, benzothiazole-4,7-diones, and 1,4-benzodioxin-5,8-diones is discussed with particular emphasis as antimetabolites of coenzyme Q (74AG635). Heterocyclic quinones were hypothesized to function as bioreductive alkylating agents in that after they undergo a reduction *in vivo* they become potent alkylating agents (77MI1).

Heterocyclic quinones are arranged in this article according to the ring size of the heterocyclic part and the number of heteroatoms present. Extended quinones, i.e., benzo- naphtho-, and quinones with two heterocyclic rings, are

discussed after the simple, parent representatives. References that have appeared by mid-1987 are included.

II. Quinones with a Condensed Four-Membered Heterocyclic Ring

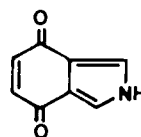
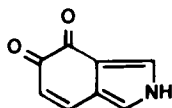
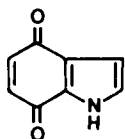
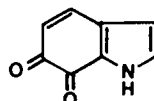
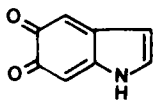
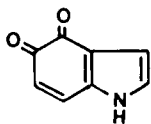
Thus far there is only one report describing such a system. A naphtho [2,3-*d*]-1,2-diazetin-4,9-dione structure has been proposed for the product **1** from the reaction between 2,3-dichloro-1,4-naphthoquinone and diphenylhydrazine (85MI1).

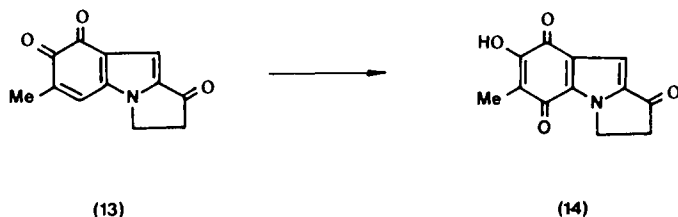
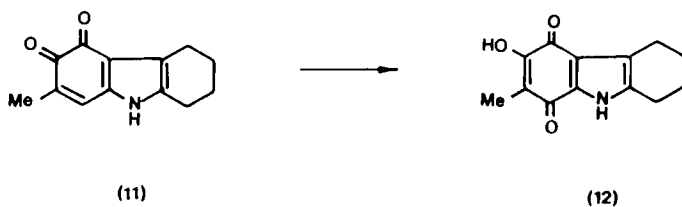


III. Quinones with a Condensed Five-Membered Ring with One Heteroatom

A. PYRROLE DERIVATIVES

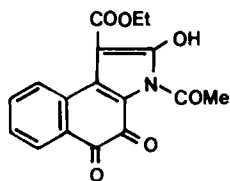
There are four parent isomeric indoloquinones: the 4,5-dione (**2**), 5,6-dione (**3**), 6,7-dione (**4**), and 4,7-dione (**5**). In the isoindole series there are two isomers: isoindole-4,5-dione (**6**) and -4,7-dione (**7**). There are many benzo, naphtho, and other extended analogs and they will be treated later. In the indole series, there are only a few representatives of systems **2-4** and the same holds for the isoindole series. However, there are many examples of **5**.



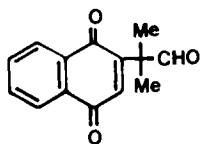


adrenochrome seems to be better represented by the zwitterionic formula. The chemistry of adrenochrome and related compounds was reviewed (59CRV181). Nevertheless, a compound with a quinonoid structure resembling **3** is the product of oxidation of the alkaloid brucine with a mixture of nitric and perchloric acid or chromic and sulfuric acid and the reaction represents a qualitative test for nitric acid or nitrates (38CB2023).

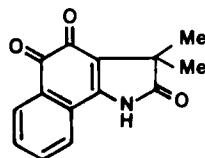
There are also few compounds corresponding to **4**. 2,3-Diphenyl-6-hydroxyindole afforded the corresponding 6,7-dione upon oxidation with Fremy's salt (61JCS3516). Similarly, the 1,2-dione was obtained from 2-hydroxycarbazole (54CB1251). By a nonoxidative procedure, the quinone **17** was obtained when 3-acetylamino-4-chloro-1,2-naphthoquinone was condensed with diethyl malonate (1899CB260). A related cyclohexyl analog was similarly prepared (85ZOR1315). In an uncommon reaction the aldehyde **18** formed a cyclic oxime, which undergoes a redox reaction in ethanolic solution to give the quinone **19**, or tautomeric form. The latter compound



(17)

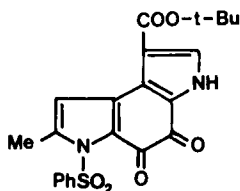


(18)



(19)

reacts with 1,2-diamines, as *o*-quinones usually do (72LA50). A bipyrroloquinone (20) was prepared from a bipyrrrole derivative and oxalyl chloride (87JA271).

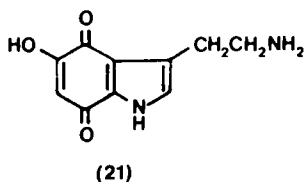


(20)

Numerous derivatives of benzo analogs of indole-4,7-dione (5) were prepared in connection with synthetic studies of mitomycins. Here again, oxidation reactions were used to generate the quinone moiety. For the most part, 4- or 7-hydroxy- and 4,7-dihydroxyindoles were used as precursors. They were oxidized by dichromate (54JCS3916; 61JCS3516; 70FES972; 75G293; 80JHC563; 81JHC613), Fremy's salt or FeCl_3 (58CB2089; 64JA3878; 66JAC804; 67JMC1, 67JMC7, 67JMC14, 67JMC23, 67JMC95; 68JMC737, 68JMC882; 71HCA2411, 71MI2), nitric acid (81JHC613), or air (78TL2251; 82JHC633). The corresponding precursors were oxidatively demethylated either with ceric ammonium nitrate (CAN) or with Ag_2O in nitric acid to

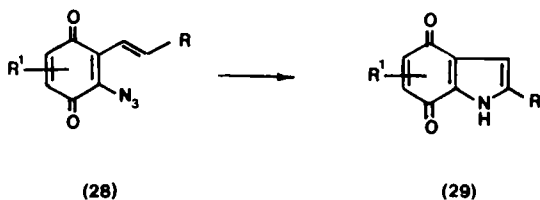
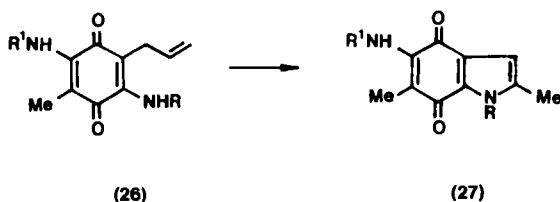
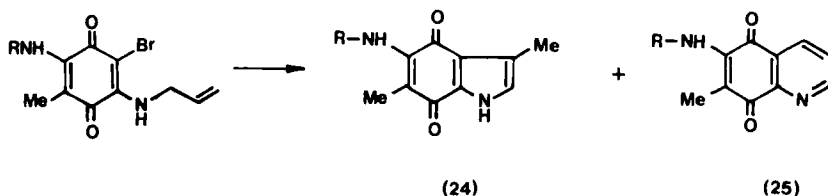
give the 4,7-dione system (76OPP293; 79JOC1536; 85CPB2122). Also, 4,5,7-trimethoxyindoles are transformed only in the corresponding 4,7-diones (85CPB2122). 5-Hydroxytryptamine, a naturally occurring chemical neurotransmitter, is oxidized electrochemically via the 5,7-dihydroxy- and 4,5,7-trihydroxytryptamine to 5-hydroxytryptamine-4,7-dione (**21**). This compound is a more potent central nervous system toxin than 5,7-dihydroxytryptamine. The antimicrobial activity of several indolequinones was examined (75FES137; 81FES622).

In addition to oxidative methods, there are several syntheses of indole-4,7-diones by cyclization. Indoloquinones **23** and their benzo analogs were prepared by ring closure of **22** or directly from the aminochloroquinone



with dialkyl malonate (73TL4695). Similarly, 2,3-dibromo-1,4-naphthoquinone reacts with diethyl malonate or an active methylene compound and a primary amine to give the linear benzolog of **23** or **5** (1900CB566; 30BCJ348). A new method has been developed that involves cyclization of ortho-substituted allylaminobromoquinones in the presence of palladium acetate and tri-*o*-tolyl phosphite in acetonitrile. The reaction takes place in the presence of Pd(0) catalyst. Yields are sometimes low and, in addition to the normal product (**24**), the reaction takes place at the terminal carbon atom of the N-allyl group giving rise to a quinolinequinone (**25**). In some cases the corresponding hydroquinones also react and are subsequently oxidized (85JOC4282). Similar results were obtained with precursors such as **26**, which are cyclized to **27** (86G213).

In connection with mitomycins, a new synthetic approach was developed. Thermal decomposition of 2-azido-3-vinyl-*p*-quinones (**28**) results in ring closure (**29**) (73CC358). Thermal cyclization does not involve a nitrene intermediate and a mechanistic interpretation has been presented (74JOC774).

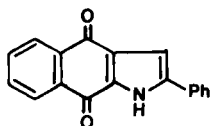


Ring closure is possible also under acidic conditions although the mechanism is not clear. The same results are obtained by photolysis (74JOC774). This method was also used for other related azidoquinones (82BCJ2922).

3-Unsubstituted 2-azido-1,4-benzo- or -1,4-naphthoquinones react photochemically with a variety of dienes to give the corresponding 2,3-dihydroindole-4,7-diones. All of these transformations are stereoselective (74JOC781; 86CL1185). Of particular interest is the observation that the major isomer always has a *cis* relationship between the substituents at positions 2 and 3 in the pyrrole part, regardless of the stereochemistry of the starting diene (74JOC781).

A new, general synthetic approach for heterocyclic quinones involves thermolysis (160°C) and subsequent oxidation by air, FeCl_3 , or CAN of 4-hydroxy-4-heteroarylcyclobutenones or 2-hydroxy 2-substituted benzo-cyclobutenones (86JOC3065). This method was used to prepare indole-4,7-diones and their benzo analogs.

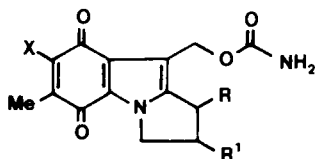
2-Phenylethynyl-3-(substituted amino)-1,4-naphthoquinones are cyclized in the presence of pyridine to the quinones **30** (85IZV1090).



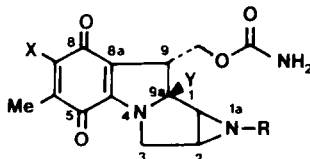
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The vast research on mitomycin antibiotics has been reviewed through 1978 (79M11) and these investigations are, in general, not included here.

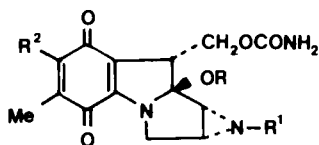
There are two groups of compounds belonging either to mitosenes (31) or mitosanes (32). Mitomycin A (33), mitomycin B (34) (76M11), mitomycin C (35), porfiromycin (36), and mitiromycin (37) (70JA2589) are a class of antibiotics active against gram-positive and gram-negative bacteria and also



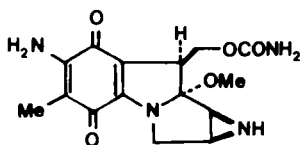
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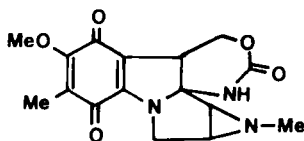
(32)



	R	R ¹	R ²
(33)	Me	H	OMe
(34)	H	Me	OMe
(36)	Me	Me	NH ₂



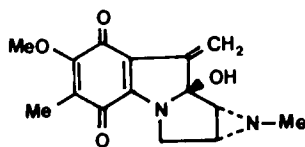
(35)



(37)

against several kinds of tumors. Mitomycin C is a significant resource in cancer chemotherapy (79MI2) and some derivatives of mitomycin C lacking the aziridine ring have been shown to inhibit cell division in bacteria (72AAC73). Structure–activity relationships of the mitomycins, some synthetic analogs, and indoloquinones were investigated (74JMC729).

The crystal structure of mitomycin C was determined by X-ray diffraction (79BCJ2334). From the structure of its *p*-bromobenzoyl derivative, the revised absolute configuration of mitomycin is now as shown in **35** (83JA7199). Mitiomycin was isolated in 1962 and has an oxazinone ring instead of an open-chain carbamate ester as present in mitomycin (62JA3184). From *Streptomyces caespitosus* fermentation broth, a new mitomycin, 10-decarbamoxy-9-dehydromitomycin B (**38**), has been isolated and its structure elucidated from spectroscopic data (81MI1). The compound could be obtained from mitomycin B with sodium hydride and some analogs were prepared (81MI3).

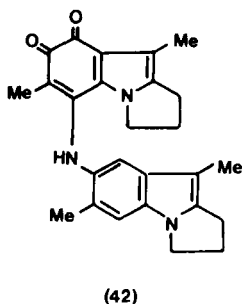
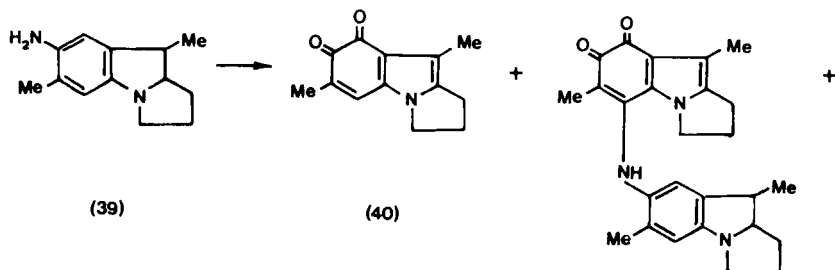


(38)

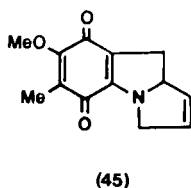
Since the first total synthesis of mitomycins A and C was described in 1977 (77TL4295), many syntheses have been devised and many analogs prepared (79MI3; 86JOC4307; 87JMC168). A 17-step synthesis of 7-methoxymitosene (**31**, $R = R^1 = H$, $X = MeO$) from 6-methylindole produced 3% overall yield (87CL1225) and other approaches have also been described (64JA3877; 65JOC2897; 87H1207). Other significant syntheses are the preparation of aziridinomitosene (86JA4648), the Polonovski reaction of certain synthetic mitosane N-4-oxides (87H301), and from leucoaziridinomitosene, a quinone with an “enepyrrole” substructure. The latter compound could not be isolated (87JA2204), but is an excellent model in the cross-linking of DNA.

Pyrolo[1,2-*a*]indoloquinones of the mitosene type (**31**) were prepared by either oxidation or cyclization. Oxidation of amino or hydroxy precursors was done mainly with Fremy's salt (72ABC106; 73TL131; 74ABC381, 74JOC3580; 85LA1422).

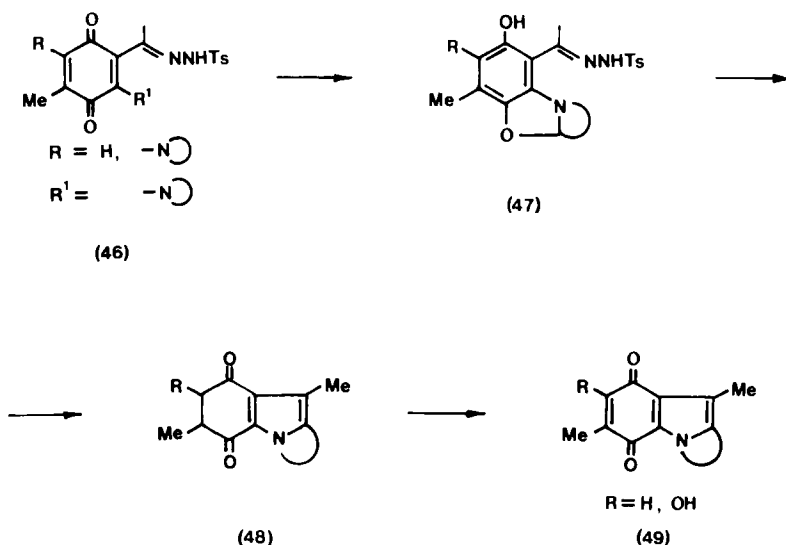
A complex reaction mixture was obtained when the amino compound **39** was oxidized with Fremy's salt. In addition to the anticipated quinone **40** (6.9% yield), the dimeric quinones **41** (2.9% yield) and **42** (4.9% yield) were also obtained. On the other hand, the aromatic analog **43** gave only **40** in 43% yield and the compound rearranged under the influence of acid into the *p*-quinone **44** (72CPB1785).



Pyrrolo[1,2-*a*]indolequinones were prepared also by cyclization reactions. One of them involves copper-catalyzed pyrolysis of 2-azido-5-methoxy-6-methyl-3-(2,4-pentadienyl)-1,4-benzoquinone to give compound **45** (87JOC3956). The second pyrrole ring was also formed from a 2-hydroxypropyl side chain of an indolo-4,7-dione (80JOC5057). Benzo analogs were prepared in a Friedel-Crafts reaction from either phthalic anhydride (67TL765) or 2-pyrrolidinyldicarbonyl chloride (86H2797).



An interesting new synthetic approach for pyrrolo[1,2-*a*]indolequinones and related systems was developed from acylaminoquinonetosylhydrazones (46). These, when photolyzed, give unstable benzoxazoline intermediates (47), which are converted via the dihydro compounds 48 into the tricyclic quinones 49 (78JOC4472). These transformations also proceed thermally and, in some cases, the intermediate (47) could not be isolated (74TL3283; 77CPB259, 77CPB543; 78JOC4472).



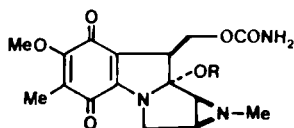
It should be mentioned that the methoxy group at position 7 of mitosanes and at position 5 of indoloquinones is readily displaced. In the presence of a small amount of base, alcoholysis occurred and the corresponding alkoxy compounds were obtained (80MI2). On the other hand, the 7-methoxy group is readily displaced in the reaction with amines to give the corresponding substituted 7-amino derivatives (86JMC1864). The 7-amino group of mitomycin C can be alkylated and acylated, preferentially in the presence of NaH (85TL3923). Mitomycin C was converted to a number of 1 α -formyl or -thioformyl derivatives (87JMC1767), whereas with trifluoroacetic acid a stereoselective aziridine ring opening occurred and a mitosene derivative (31, R = OH, R' = NHCOCF_3 , X = NH_2) was obtained. This transformation is postulated to proceed via a carbonium ion (87H577).

Reactivity of the C-10 methylene unit in mitosenes toward both nucleophiles and electrophiles has been demonstrated (86JA296). The $-\text{CH}_2\text{OCONH}_2$ side chain is readily transformed into a methyl group

upon hydrogenation and subsequent oxidation. It has been shown that deuterium incorporation at C-10 takes place only from O-deuterated alcohol, but not from D_2 .

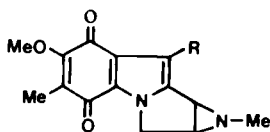
Mitomycin C and certain mitosene derivatives were reduced catalytically or by electrochemical reduction (86JA4158; 87JA1833; 87T255). These reductions do not affect the quinone part.

Mitomycin F (**50**), when reduced under anaerobic conditions, is transformed into the leuco compound, the quinol. This, when chromatographed in the presence of air, gives, in addition to **50**, also aziridinomitosenes **51** and 9-epimitomycin (**52**). The structure of the latter compound was established by X-ray analysis. When access to oxygen was minimized, only traces of **53** and **54** were obtained (87JOC4424).

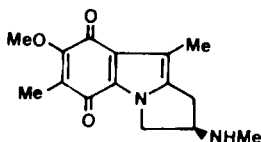


(50) R = Me

(52) R = H

(51) R = $-\text{CH}_2\text{OCONH}_2$

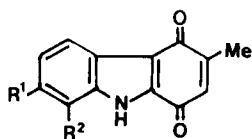
(53) R = Me



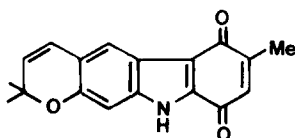
(54)

Mitomycin C forms a weak association with metal ions and these metal complexes undergo rearrangement to mitosenes in methanol (86JMC144). Complexes were also tested for antitumor activity (86JMC1760).

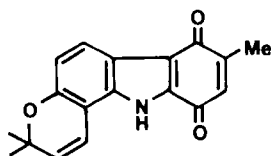
Among other extended quinones, derivatives of carbazolequinone should be mentioned. Such compounds can also be found in nature, and from root bark of *Murraya euchrestifolia* the following isomeric compounds were isolated (from 900 g of dried bark): murrayaquinone-A (**55**) (3 mg), murrayaquinone-B (**56**) (95 mg), murrayaquinone-C (**57**) (15 mg), and murrayaquinone-D (**58**) (5 mg) (83H1267; 85CPB4132). From the same plant, pyrayaquinone-A (**59**) and pyrayaquinone-B (**60**) have also been isolated in 0.0002



	R ¹	R ²
(55)	H	H
(56)	OMe	prenyl
(57)	OMe	geranyl
(58)	OH	geranyl



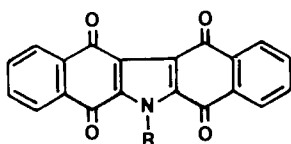
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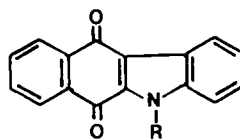
(60)

and 0.0003% yield (85CPB1320). Both compounds, as well as murrayaquinone-B and murrayaquinone-A, have also been synthesized (84CI(L)614; 85CC1391, 85CPB1320).

As with indolequinones, carbazolequinones were prepared by oxidation of appropriate amino or hydroxy precursors (50MI1; 59CB2385). They are also formed through cyclization, (i.e., 1,4-benzoquinones react with alkylamines to produce the disubstituted benzoquinones as well as carbazolequinones) (69BCJ2043; 79M51). In a similar manner, substituted amino 1,4-naphthoquinones are oxidized with potassium persulfate first into dimers, which may subsequently cyclize into carbazolediquinones **61**, whereas 2-arylamino-1,4-naphthoquinones gave compounds **62** (75JCS(P1)1115). A derivative of **62** was also obtained in an unusual transformation from benzanthracenequinone, which was found to be a key intermediate in the biosynthetic pathway of kanamycin (87JA5282).

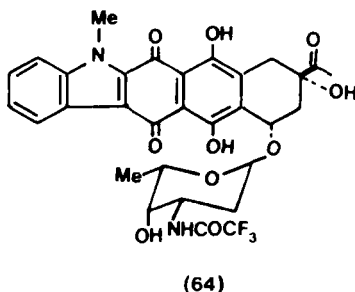
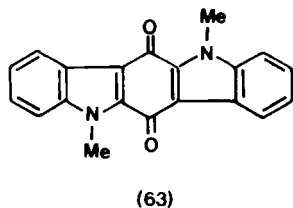


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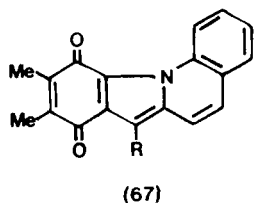
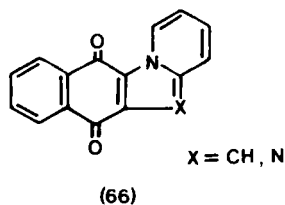
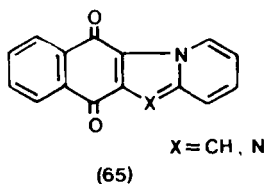


(62)

The pentacyclic derivative of indolo[3,2-*b*]carbazole-6,12-dione **63** was prepared from 1-methylindole-2-carbonyl chloride in the presence of AlCl_3 (63JOC2930). Total synthesis of an indole analog of daunomycin has been accomplished via a strong base-induced cycloaddition of hetero-fused pyran-diones. Glycosidation gave a mixture of glycosides, from which the natural-type (9*S*,11*S*)- α -glycoside **64** was obtained (87CC1474).



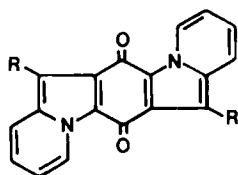
There are several representatives of fused indolequinones having a ring junction nitrogen atom. A general approach for the linear (**65**) or angular systems (**66**) or their benzo analogs consists in treatment of the corresponding 2,3-dihalo-1,4-naphthoquinones with reactive methylene compounds in the presence of pyridine ($\text{X} = \text{CH}$) or 2-aminopyridine ($\text{X} = \text{N}$) (53M11; 54JOC176, 54PIA(A)185; 57JA1212; 58M11; 59JOC374; 61JOC1316; 63JOC3502). Similarly, a substituted 2,3-dibromo-1,4-benzoquinone reacts to give **67** in the presence of quinoline (87M13). In a different approach, the tetrahydro analogue of **65** ($\text{X} = \text{N}$) was prepared from 2,3-diaminonaphthalene and δ -valerolactone after subsequent oxidation (59JOC419).



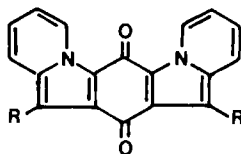
1,4-Benzoquinone reacts with acetylacetone in the presence of pyridine to give a product for which an indacene structure was first postulated (27BSF1094) and later corrected to **68** (55CI(L)1635). Further investigations have shown that reaction with 2,3,5,6-tetrachloro-1,4-benzoquinone can give a tricyclic product (reaction with only two chlorines at one side of the starting quinone) or a mixture of the linear (**68**) or angular (**69**) isomer (54JOC176; 56MI1; 57JA1212, 57JOC1641).

The bisquinone **70** was obtained by condensation of 2-anilino-3-chloro-1,4-naphthoquinone with sodium sulfide and 2,3-dichloro-1,4-naphthoquinone. The product, a pentacyclic thiazine, lost sulfur upon heating to give **70**. This diquinone can be reduced with SnCl_2 and subsequent oxidation with air yielded the monoquinone **71** (23CB1291).

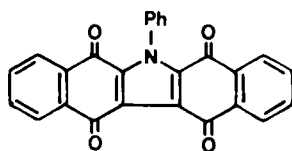
Finally, quinones of the type **72** are formed upon isomerization of binaphthalenes in boiling acetic acid (86ZOR836).



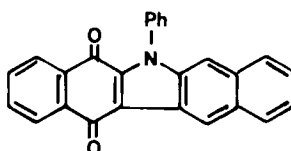
(68)



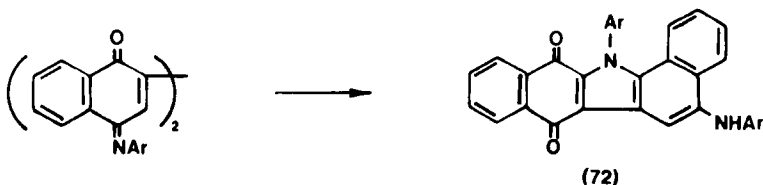
(69)



(70)



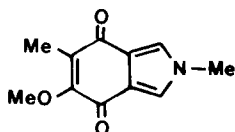
(71)



(72)

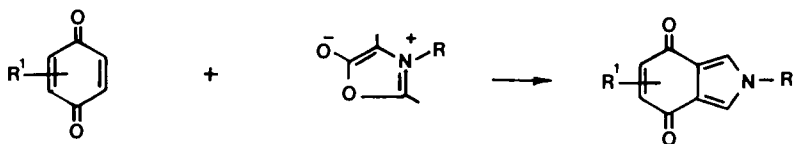
Isoindole Derivatives

Compounds belonging to this system are less abundant. Only one natural product has been isolated so far from natural resources. The quinone **73** was isolated from the sponge *Reniera* sp. in 0.001% yield (82JA265).

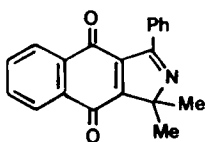


(73)

Cyclization and cycloaddition are the preferred synthetic methods for this skeleton. 1,4-Benzoquinones react in a 1,3-dipolar cycloaddition reaction with mesoionic heterocycles, as, for example, in the synthesis of **74** (86JHC1267; 87JHC971). Similarly, nitrile ylides, generated by photolysis of substituted azirines, can be used (72CB1258; 74HCA2634). A detailed investigation revealed the following regularities. 2,2-Dimethyl-3-phenyl-2*H*-azirine, transformed upon irradiation into the corresponding nitrile ylide, reacted with 1,4-naphthoquinone to give the adduct **75**. With 2-methyl- and 2,3-dimethyl-1,4-naphthoquinone, cycloaddition occurs preferentially on the carbonyl group and with 1,4-benzoquinones this reaction occurs exclusively to give spirooxazolines (83HCA2252). This contrasts with the cycloaddition with 2,3-diphenyl-2*H*-azirine (83CC51).

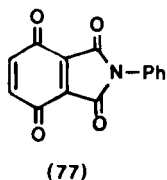
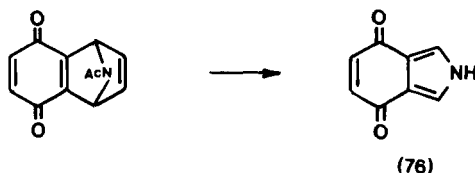


(74)



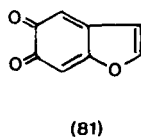
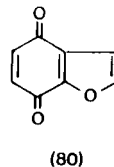
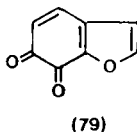
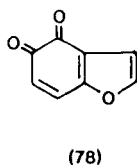
(75)

The parent quinone **76** was prepared from a tricyclic quinone and a 3,6-disubstituted 1,2,4,5-tetrazine (75JCS(P1)1339). The quinone is a stable derivative of the unstable isoindole. Substituted derivatives were also prepared (74CC1034). Quinone **77**, prepared from the corresponding hydroquinone and nitrogen dioxide, was used for cycloaddition studies. It showed high reactivity toward electron-rich dienes and trienes and the selectivities are discussed in terms of frontier molecular theory (81JA5211). Treatment of 2,3-bis(methylthiomethyl)-1,4-naphthoquinone with methylamine gave as major product the benzo analog of **74** (80JCS(P1)282).



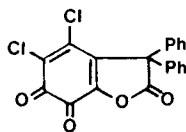
B. FURAN DERIVATIVES

Of the three isomeric furanoquinones (**78–80**), the vast majority of known quinones belongs to the *p*-quinonoid system (**80**). Representatives of the 5,6-dione system (**81**) are practically unknown.



The 4,5-diones (**78**) and their benzo analogs can be prepared by the standard oxidation procedure from 4- or 5-hydroxy precursors (70MI1; 75KGS894) or by cyclization (87TL4675). A 1,4-benzoquinone, when condensed with an enamine and after subsequent oxidation of the phenol with Fremy's salt, or less economically with benzeneseleninic anhydride, gives derivatives of **78** (87TL3427). The parent quinone **78**, prepared in this manner, is a stable compound and readily reacts with dienes to give a variety of extended furan-4,5-diones. In a typical transformation of *o*-quinones, alkali treatment of derivatives of **78** causes their conversion into 5-hydroxy-4,7-diones (cf. **80**) (70MI1).

There are only few representatives of **79**. When 2,3-diphenyl-7-hydroxy-benzofuran was oxidized with Fremy's salt, a mixture of the 6,7- and 4,7-dione was obtained (70MI2). Similarly, nitric acid oxidation of the dihydroxy precursor afforded the quinone **82** or the related 5,6-dione, corresponding to the system **81** (12LA384).



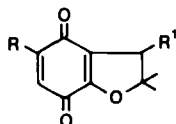
(82)

There are few derivatives of the benzofuran-4,7-dione system isolated from natural sources. From the Australian blackwood *Acacia melanoxylon*, the allergen acamelin has been isolated and its structure determined by X-ray analysis (80TL149; 81MI2). Acamelin is 2-methyl-6-methoxy-4,7-benzofurandione and several syntheses are known (83JCS(P1)2423, 83JOC127; 85CC1543). Some related naphthofuranoquinones were isolated from wood of *Paratecoma peroba* (68N38).

Synthetically, they were in general prepared from the hydroxy- or amino-benzofurans with Fremy's salt (67JCS(C)310; 76LA1487; 77CPB2535; 78JOC3063; 82AJC1665; 82MI2; 83AJC1263), nitric acid (38CB106; 62RTC810; 72BSF163; 75KGS894; 76KGS879), dichromate, or chromic acid (58ZOB78; 61G90; 77ZN(B)1084). There are a few cases in which the benzene ring-unsubstituted benzofuran is oxidized at position 4 or 7 into the quinone. In this manner, benzofuran-5-carboxylic acid or its amide was oxidized by nitric acid into the quinone (82MI3). Also khellinone is transformed after nitric acid oxidation into 5-acetyl-6-hydroxybenzofuran-4,7-dione (38CB106). 3-Carbethoxy-2-methylbenzofuran-4,7-dione was prepared from a substituted hydroquinone by oxidative cyclization with dichromate

or Ag_2O (71HCA959). The compound is labile in alkali and does not undergo cycloaddition with butadiene. Several substituted **80** derivatives were obtained in connection with structural studies and transformations of mikrolin and gilmicolin (78HCA2002; 79HCA1129).

A new cyclization approach consists of the rearrangement of 4-heteroaryl-4-hydroxycyclobutenones and subsequent oxidation by either CAN, Ag_2O , FeCl_3 , or air (86JOC3065, 86JOC3067). There is also one report of benzo-furan-4,7-dione synthesis by cycloaddition of nitrile oxides to 1,4-benzoquinones (83BCJ3457). An interesting migration of a bromine atom was established by X-ray determination of the product (**83**, $\text{R} = \text{Br}$, $\text{R}^1 = \text{OMe}$) obtained by treatment of **83** ($\text{R} = \text{H}$, $\text{R}^1 = \text{Br}$) with a deficient amount of silver oxide in methanol (81CSC1105). The ^{13}C -NMR spectrum of 3,5-dimethylbenzofuran-4,7-dione has been reported (76T1431).

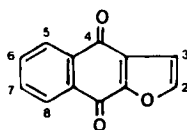


(83)

R	R ¹
H	Br
Br	OMe

1. Tricyclic Systems

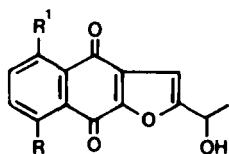
There are many natural naphthofuranquinones which have been isolated from various plants. From *Lanthana achyranthifolia* from Mexico, which is used in folk medicine as a tea for stomach disorders, diodantunezone, an 8-hydroxy derivative of naphtho[2,3-*b*]furan-4,9-dione (**84**) was isolated (83MI1). The 3,5-dimethyl derivative of **84** is maturinone, isolated from roots of *Cacalia decomposita*. At first it was not clear if the compound is a 3,8- or 3,5-dimethyl isomer (64T2331; 66T685; 69BSF3612), but later syntheses confirmed its structure as the 3,5-dimethyl isomer (69JCS(C)1184, 69TL1929;



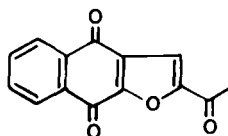
(84)

77BCJ961). From the same plant, maturone was isolated (64T2331; 66T685). It is a 3-hydroxymethyl-5-methyl derivative of **84** and it has also been synthesized (86TL3935). 5,6,7,8-Tetrahydromaturinone was also isolated from *Cacalia delphiniifolia* (76CL73).

Among other compounds from *Kigelia pinnata*, kigelinone (**85**) was isolated (81P2271). A related compound, **86**, was proposed for one of the cytotoxic compounds isolated from the bark of *Tabebuia cassinoides*. Two other compounds isolated from *K. pinnata* are **87** and **88**, and the structure of the latter was confirmed by synthesis (82MI4).



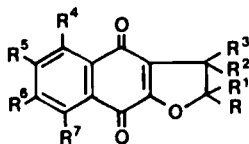
	R	R'
(85)	OH	H
(86)	H	OH
(87)	H	H



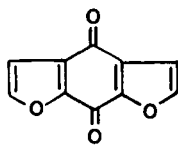
(**88**)

Two naphthofurandiones, namely the 2-ethyl derivative of **84** and **89**, were isolated from heartwood of *P. peroba*, in addition to lapachol, lapachone, and benzochromendiones (68N38). Related quinones **90** (mixtures of enantiomers) were isolated from wood of *Rademachera sinica* (81JCS(P1)2764). Helicquinone (**91**) was isolated from *Helicteres angustifolia* (87P578) and haemoventosin (**92**), a colored compound, was isolated from a lichen, *Haematomma ventosum* (71ACS483).

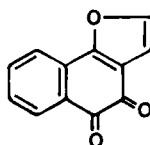
Many quinonoid pigments were isolated from Cyperaceae, a large family of monocotyledons. A survey of over 100 species from 29 genera of Australian Cyperaceae was published (78P263). Among them many contain a furan ring and are derivatives of **80** or of the cyperaquinones (**93**) (73TL3; 78P263).



	R	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷
(89)		H	H	H	H	H	H	H
(90)		H	H	OR	H	H	H	H
(91)	H	H	H	Me	Me	Me	H	OH
(92)	H	Me	H	H	OH	H	COOMe	OH
(97)	Me	Me	H	Me	H	H	H	H
(98)	H	Me	Me	Me	H	H	H	H
(115)	H	OH	Me	Me	H	H	H	H



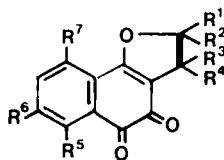
(93)



(94)

There are also few natural products derived from the angular system, naphtho[1,2-*b*]furan-4,5-dione (**94**). In response to infection by *Phytophthora* sp., the mangrove species *Avicennia marina* produces phytoalexins, of which three are derivatives of **94**: the parent quinone and its 3-hydroxy and 2-hydroxyisopropyl derivative (85P2877). Dunnione is an orange-red pigment, isolated from *Streptocarpus dunnii*; an angular structure (**95**) was first proposed (38N(L)147; 39JCS1522; 40JCS1493). Later, from synthetic experiments, the structures of α - and β -isodunnione as well as of α -dunnione have been established (48N(L)178; 50MI2, 50MI3). α -Dunnione is transformed with concentrated sulfuric acid into β -isodunnione (**96**), which is readily interconvertible to α -isodunnione (**97**) (50MI2). Later, in addition to dunnione, several prenylated analogs were isolated (82CPB2265; 83P737). These are α -dunnione (**98**), dehydrodunnione (**99**), and the hydroxydunniones **100** and **101**. These two compounds were also synthesized and were obtained together with a small amount of their rearranged products, **102** and **103** (86MI2).

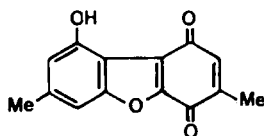
Other quinones related structurally to dunnione were isolated from *Trypethelium eluteriae* (80LA779). The proposed structures for the anti-



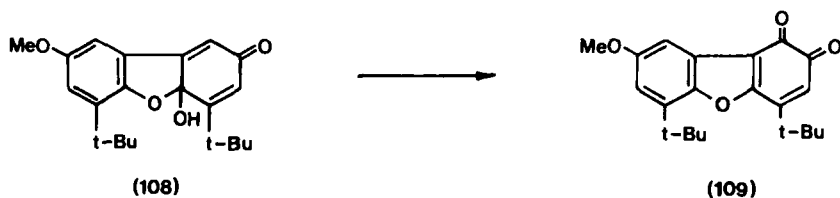
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷
(95)	H	Me	Me	Me	H	H	H
(96)	Me	Me	H	Me	H	H	H
(99)	=CH ₂		Me	Me	H	H	H
(100)	H	Me	Me	Me	H	OH	H
(101)	H	Me	Me	Me	OH	H	H
(102)	Me	Me	H	Me	H	OH	H
(103)	Me	Me	H	Me	OH	H	H
(104)	H	Me	Me	Me	H	OH	Me
(105)	H	Me	Me	Me	H	OMe	Me
(106)	H	Me	Me	Me	OMe	OMe	Me

biotically active tryptethelone (**104**) and its methoxy (**105**) and dimethoxy (**106**) analog have been confirmed by synthesis (84JOC1853). Compounds were prepared by cycloaddition of vinylogous ketene acetals to appropriate 1,4-benzoquinones. The reaction proceeds regiospecifically in essentially one step.

Synthetically, two main approaches have been applied: the formation of the quinonoid part on oxidation and, more frequently, via cyclization. Oxidation of 4,5-dihydroxy-2,7-dimethyldibenzofuran with Fremy's salt resulted in formation of **107**; even with excess of the reagent, only one part of the molecule is converted into the quinone (59CB1416). Quinone **109** was obtained either from the 2-hydroxy precursor and Fremy's salt or from the hemiacetal **108** after treatment with perchloric acid (66JCS(C)362). Difuran-quinone **93** was obtained by chromium oxide oxidation of the 8-methoxy precursor (66LA123) and this reagent was applied also in related cases (44JCS56). The 2-methyl analog of **94** was prepared from the 5-hydroxy precursor with various oxidants, the yield being best when Fremy's salt was used (67JCS(C)2126).

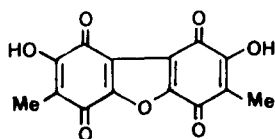


(107)

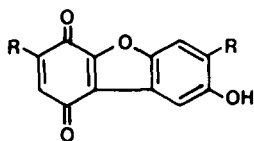


Phoenicine, a bis-1,4-benzoquinone derivative, was transformed by oxidative cyclization to the tetrone **110** (38HCA1326; 43HCA2031). The deshydroxy analog of **110** was obtained by thermal cyclization (61CB356). Cyclization of a bis(1,4-benzoquinone) derivative was achieved also thermally above 200°C to give quinones of the type **111** (34MI1). Isolapachol (**112**, R = H), when oxidized with mercuric acetate, is transformed into a mixture of the angular (**113**, R = H) and linear (**114**, R = H) quinones. The latter is also obtained from acid-catalyzed isomerization of **113** (R = H) (67JOC2341). The 8-hydroxy analog **112** (R = OH) was cyclized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give three compounds, quinones **113** (R = OH) and **114** (R = OH) being the minor products (80TL5083). A mixture of the 2-methyl analogs of **113** and **114** was similarly obtained by oxidative cyclization with DDQ, the linear quinone being the major product (87JMC2005).

The formation of the furan ring by cyclization of a side chain has also been an efficient method in several cases. Simultaneous formation of the

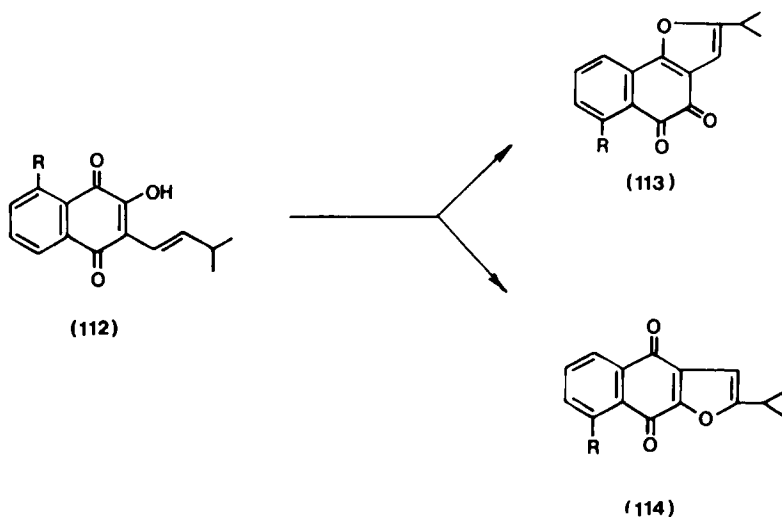


(110)



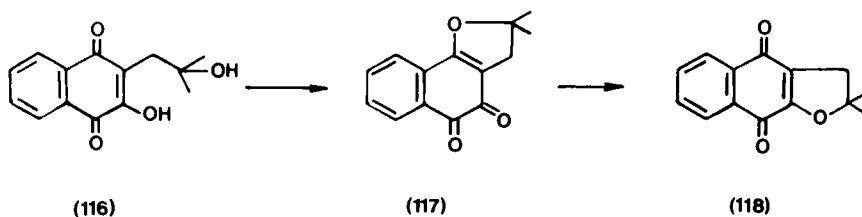
R = Me, MeO

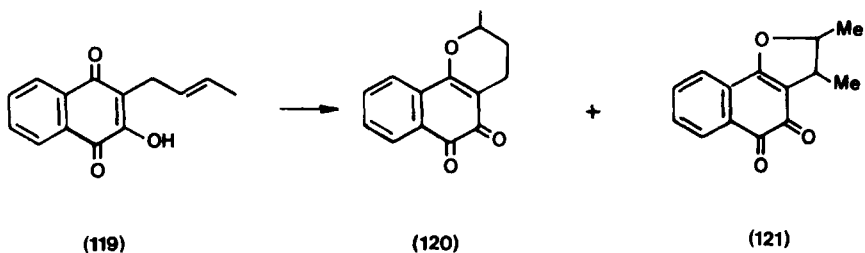
(111)



naphthalene and furan rings was achieved when a substituted phenyl acetylsuccinate is cyclized with sulfuric acid and the alkaline solution of the product exposed to air to give the red 2-hydroxy-3-methyl derivative of **84** (54JCS4655). In another case, a substituted acetaldehyde side chain, attached to 1,4-naphthoquinone, after treatment with bromine in chloroform gives **115** (72LA28). Analogs of the angular system **94** were prepared similarly (74CJC88).

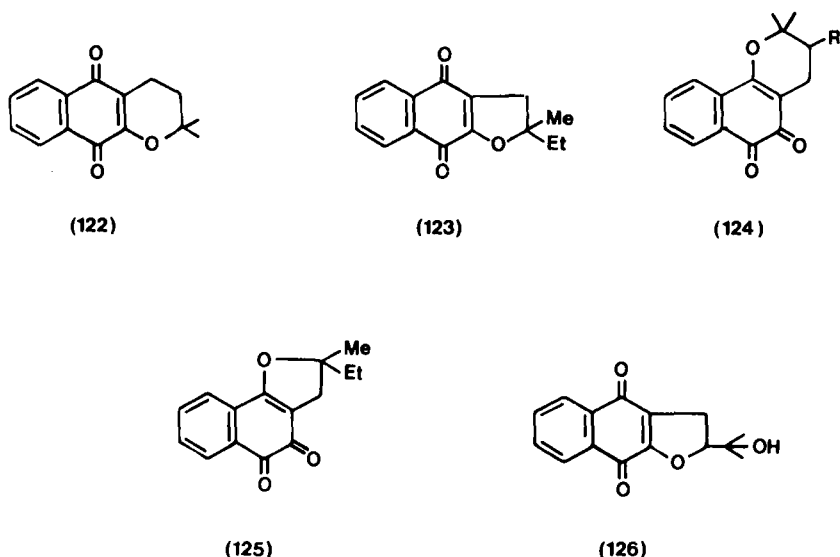
Hooker discovered in his classical experiments that from substituted 1,4-naphthoquinones, such as **116**, the angular quinone **117** is formed and is isomerized under the influence of acid into the linear quinone **118** (1896JCS1357; 36JA1168, 36JA1202). The furan ring is also formed when the ortho positions of a quinone are substituted by a hydroxy and an allyl group, and again a mixture of angular and linear quinones is formed (26JA3201; 28JA465). When a crotyl group is present, a pyran or a furan ring can be formed. For example, **119** is transformed in concentrated sulfuric





acid into a mixture of **120** and **121** (27JA857; 41JA2948). Isoprene, when condensed with 1,2,3,4-tetrahydroxynaphthalene, after oxidation gave a mixture of lapachol and an isomeric compound. Both were cyclized in the presence of acid into α -lapachone (**122**) and the furoquinone **123**. With concentrated sulfuric acid, however, β -lapachone (**124**, R = H) and the angular quinone **125** were obtained (48JA614). A similar transformation was observed when an orange pigment, stenocarpoquinone A, a 3-hydroxy- β -lapachone (**124**, R = OH), was transformed into the bromo derivative (**124**, R = Br) and treated with alkali. This caused ring opening and the resulting glycol was cyclized in the presence of acid into the furan derivative **126** (73AJC1121).

Tricyclic furanquinones were also obtained from cycloaddition reactions. 3-Methylbenzofuran-4,7-dione reacts with piperylene in a Diels–Alder reaction to give a mixture of maturinone and its isomer, a 3,8-dimethyl derivative of **84** (69TL1929).



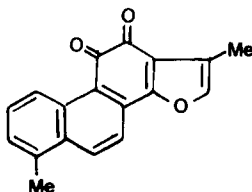
In a similar manner, 3-methylnaphtho[2,3-*b*]furan-4,9-dione was prepared from 2-acetoxy-1,4-naphthoquinone in a Diels–Alder reaction (70BCJ824). However, if the reaction was carried out in nitrogen atmosphere, a furonaphthalene derivative is formed and this could be transformed into the angular 3-methylnaphtho[1,2-*b*]furan-4,5-dione (70BCJ824).

Many furanquinones, derivatives of **84**, were formed in the reaction of 2,3-dichloro-1,4-naphthoquinone with reactive methylene compounds in the presence of various basic reagents. The reaction can proceed in one step or by a two-step route via 3-substituted 2-chloro-1,4-naphthoquinones (1900CB2402; 53P1A(A)534; 57JA5489; 65JOC3819; 71ZOR1031).

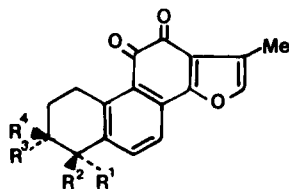
2. Tetracyclic Systems

Among a large group of natural tetracyclic furanquinones, isolated from dried roots of *Salvia miltiorrhiza*, is a clinically important Chinese drug, Dan-Shen, used in treatment of heart diseases. More than 16 orange-red pigments have been isolated and they are classified in two groups according to their structural characteristics (i.e., with an *o*- or *p*-quinone skeleton). Among these are tanshinone-I (**127**), tanshinone-IIA (**128**), tanshinone-IIB (**129**), and cryptotanshinone (**130**). These structures were proposed from degradative studies, from spectroscopic data, and by syntheses (34MI2; 40CB19; 41MI1, 41MI2; 42CB617, 42CB958; 61BCJ895; 68JCS(C)48; 71MI1; 85MI2). Among minor components are tanshindiol A (**131**), tanshindiol B (**132**), tanshindiol C (**133**), nortanshinone (**134**), 3- α -hydroxytanshinone (**135**), and methyl tanshinoate (68TL3231; 85P815). Tanshinone-I was synthesized either by annelation of the furan ring (74CJ88) or by Diels–Alder synthesis from 3-methylbenzofuran-4,7-dione, and this principle was applied also for the preparation of cryptotanshinone and tanshinone-II (68CC1327; 69BCJ3318).

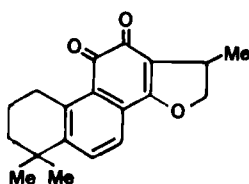
The bisoynthetic pathway for cryptotanshinone has been determined experimentally by incorporation of labeled glucose in the molecule, and the absolute configuration at C-15 has been determined (87CC1311).



(127)



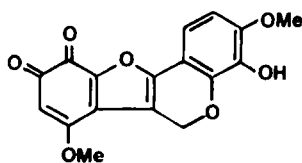
	R ¹	R ²	R ³	R ⁴
(128)	Me	Me	H	H
(129)	Me	CH ₂ OH	H	H
(131)	CH ₂ OH	OH	H	H
(132)	Me	OH	OH	H
(133)	Me	OH	H	OH
(134)		O	H	H
(135)	Me	Me	OH	H



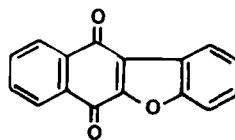
(130)

Bryaquinone (136) is the principal purple pigment in the heartwood of *Brya ebenus*. It was isolated together with a small amount of the 4-desoxy analog (75JCS(P1)1113).

The oxidative formation of the quinone part was used also for the preparation of some benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones [brasanquinones (137)] (03CB2199, 03CB2202; 08CB2373; 09JCS398; 70JIC567) or analogous systems (78CJC517).



(136)



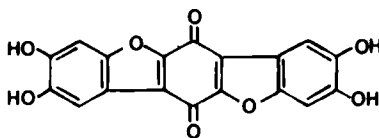
(137)

Furanquinones were formed also by acylation of the quinone moiety and subsequent ring closure. Derivatives of **137** were prepared in this fashion (53E256; 54JIC101; 61JCS1167; 63JIC203; 65JIC205; 70JIC567).

In another method, 2,3-dichloro-1,4-naphthoquinone reacts with resorcinol to give 3-hydroxy-**137** (1899CB924; 47CB47). The transformation of a naphthoquinonespirocyclopentadiene adduct, which is converted with methanolic sodium hydroxide into a furanquinone derivative as a minor product (72CC1332), represents a particular case.

3. Pentacyclic and Higher Systems

Thelephoric acid is a pigment found in several species of *Thelephora* or *Hydnum* fungus in about 0.6%. Two erroneous structures were proposed, first in 1930 by Kögl and later in 1959 by Read and Vining. In 1960, Gripenberg succeeded in elucidating the correct structure (**138**) (60T135). The enolizable system explains the relatively strong acidity of the acid. The structure is also supported by synthesis from 2,3,5,6-tetrachloro-1,4-benzoquinone and two molecules of 3,4-dimethoxyphenol, followed by demethylation (60T135). Alternatively, a Michael addition of catechol to 2,5-dihydroxy-1,4-benzoquinone afforded the acid in 3% yield (64AG313). Cyclization of a trisbenzoquinone gave the same system (65ACS540).

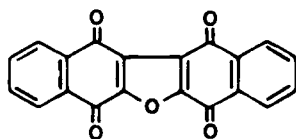


(138)

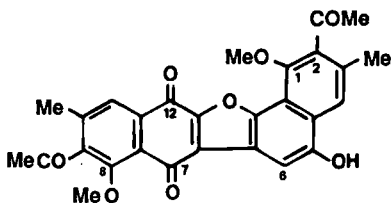
From roots of *Daniella revoluta*, a bisnaphthoquinone pigment, dianelinone, was isolated. The compound is easily transformed into a dinaphtho [1,2-*b*: 2'-*d*]furan-7,12-dione upon irradiation in chloroform or ethanol (65AJC218).

Oxidation of 2-dimethylamino-1,4-naphthoquinone with potassium persulfate afforded the bisquinone **139** (34MI1; 75JCS(P1)1115). The first step in this transformation is the oxidative coupling to the dimer. A pentacyclic compound of the system **140** was obtained by irradiation of 2,2'-binaphthalene-1,4; 1',4'-diquinone (61CB2726), or simply by heating in high-boiling solvents (39CB1623). The same pentacyclic system was also obtained by ring closure of the quinone part via an acyl chloride (63CB1167).

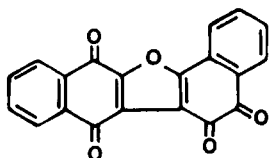
3,3'-Dihydroxy-2,2'-binaphthalene is transformed into **139** upon dehydration. The compound is obtained along with a small amount of both *o*-quinones **141** and **142** in hot acetic and sulfuric acid. However, compound



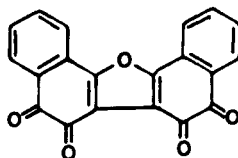
(139)



(140)



(141)



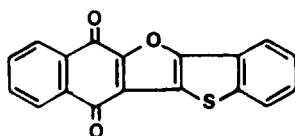
(142)

141 becomes the main product if dehydration takes place at room temperature in the presence of concentrated sulfuric acid (36JA1212).

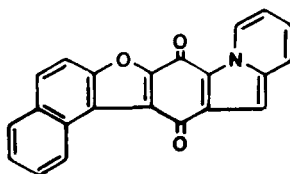
The examples above represent the well-known rearrangement of diquinones to furanquinones that takes place thermally or photochemically (34MI1; 39CB1623; 63T1919). In alkaline solution the red furanquinones give blue or green color and this has been attributed to cleavage of the furan ring and anion formation (63T1919). Furanquinones **140** were synthesized also from 2,3-dichloro-1,4-naphthoquinone and naphthols (51JCS2871, 51JOC185; 52JCS489, 52JCS4699, 52JOC243; 53JOC4, 53JOC582; 55JCS2776, 55JOC1191, 55MI1; 56JOC21; 57JCS4994, 57MI1, 57MI2, 57MI3; 59JOC1756; 61JOC3152; 85MI10). Sometimes mixtures of isomeric systems are formed. A thianaphthene analog (**143**) was prepared similarly from 3-hydroxybenzo[*b*]thiophene (65JCS2646). Hydroxyquinolines, hydroxyisoquinolines, or 4-hydroxycoumarin or its benzo analogs reacted in an analogous manner (56JCS1743, 56JOC1022; 65JCS6105). It was shown that 1-naphthols are more reactive than 2-naphthols for furan ring formation (63T1919) and the reaction mechanism of these transformations was studied (63G123).

An analog of **138** was prepared in low yield by a Friedel–Crafts reaction between 1,4-benzoquinone and veratrole (33CB792).

Derivatives of **138** and some heptacyclic analogs were prepared from 2,3,5,6-tetrachloro-1,4-benzoquinone and phenols (57JOC342, 57MI2; 60T135). When present, pyridine is incorporated into the newly formed molecule, and quinones like **144** were obtained (58MI2).

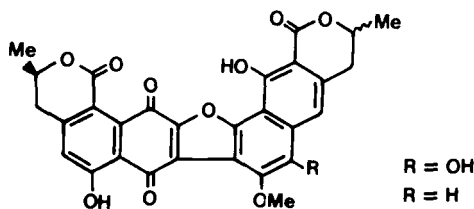


(143)



(144)

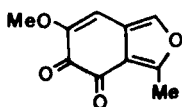
Several quinonoid pigments were isolated from the mycelium of *Aspergillus*. In addition to the known xanthomegnin, two heptacyclic heterocyclic quinones, viopurpurin (**145**, R = OH) and rubrosulphin (**145**, R = H), were isolated. For viopurpurin, which was previously isolated from *Trichophyton violaceum*, another structure was proposed (66CJC2873; 69CJC1223), but chemical and spectroscopic evidence favor the revised structure (**145**, R = OH) (75JCS(P1)163).



(145)

4. Isobenzofuran Derivatives

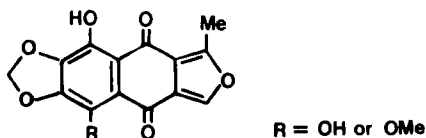
There are few natural representatives of this system. Albidin is a fungistatic red pigment isolated from *Penicillium albidum* and an X-ray analysis has shown that it has structure **146** (86JCS(P1)1145). From the fungus *Nectria haematococca*, in addition to the previously known quinones, a new one, nectriafurone (**147**), was isolated (83P1301). From 2.5 kg of the root bark of



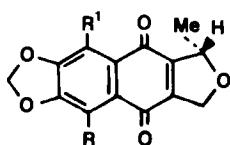
(146)



(147)



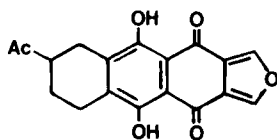
(148)



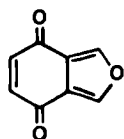
	R	R¹
(149)	OMe	OH
(150)	OH	OMe
(151)	OMe	OMe

Ventilago maderaspatana, five furanquinones were isolated in the amount of 18–65 mg each and named ventilonones A–E (**148**–**151**). The structure of ventilone C was confirmed by X-ray analysis (85T635).

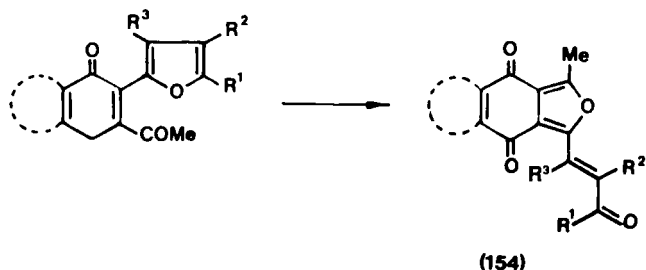
Synthetically, compound **152** was prepared by the Friedel–Crafts procedure from furan-3,4-dicarbonyl chloride and a tetralin derivative (85JCR (S)338). 1,4-Dihydro-1,4-epoxy-5,8-naphthoquinone, when treated with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, yielded the quinone **153** (75JCS(P1)1339); derivatives of **153** are also known (74CC1034). The parent compound (**153**) is a stable derivative of the unstable isobenzofuran. Finally, 3-acetyl-2-furyl-1,4-benzo- (or -naphtho-) quinones are isomerized photochemically in aprotic solvents into the quionones **154** (66HCA1806).



(152)

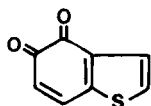


(153)

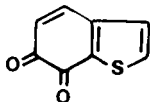


C. THIOPHENE DERIVATIVES

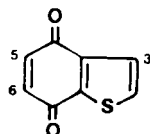
The vast majority of this class of compounds belongs to the benzo-thiophene-4,7-dione system (**157**), whereas compounds belonging to the benzo-thiophene-5,6-dione system are so far unknown.



(155)



(156)

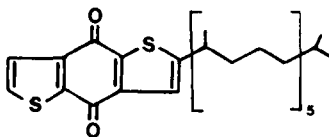


(157)

Derivatives of benzothiophene-4,5-dione (**155**) are prepared by oxidation of the 5-hydroxy precursors and the same holds for some extended systems (36LA83; 53CB366; 53JCS4186). The previously described 3-bromo compound (36LA83) is in fact 6-bromobenzothiophene-4,5-dione and oxidation of 4,6-dibromo-5-hydroxybenzothiophene with nitric acid involves also the replacement of the bromine atom at position 4. This is also the case with related compounds (56JA5351, 56JA177; 60JCS938). The potassium 7-sulfonate of **155** is transformed in methanol in the presence of sulfuric acid into the 5-methoxy derivative of **157** (35JA1611).

Oxidation of 3-phenyl-7-hydroxybenzothiophene with Fremy's salt afforded, in almost equal amounts, 3-phenyl derivatives of **156** and **157** (70MI3). Difficulties were encountered in the preparation of quinones from substituted alkyl benzothiophenyl-3-acetates. The only successful conversion of ethyl 6-hydroxy-5-methoxybenzothiophenyl-3-acetate was in a two-phase system with either aqueous periodate or thallate. The quinone was obtained in low yield (79JHC231). Some extended analogs could be prepared directly from the hydrocarbons with chromic acid (53CB366; 56JCS3435).

The first natural benzothiophene quinone, a derivative of **157**, was isolated in 0.055% yield from cells of *Caldariella acidophila* in a volcanic area of Naples (75CC392). Sulfur-metabolizing archaeobacteria are of special interest because they grow under extreme conditions of pH and/or temperature. The above compound, caldariellaquinone, is a derivative of **157** with a methylthio group at position 5 and a C₃₀ isoprenoid side chain at position 6 (77JCS(P1)653). Caldariellaquinone was isolated also from the anaerobically grown archaeobacterium *Sulfolobus ambivalens*, together with some lower homologs and a 5-methyl analog (83MI2; 86MI3). Caldariellaquinone is also the main compound (94%) found in *Sulfolobus solfataricus* and is accompanied by a 5-methyl analog (5%) and **158** (0.2%) (86CC733; 86MI4).

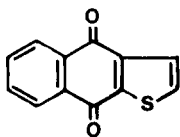


(158)

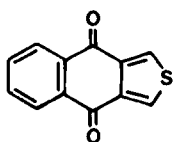
Synthetically, derivatives of **157** are prepared by oxidation of the 4,7-dihydroxy or aminohydroxy precursors with dichromate (35JA1611; 45JA1645) nitric acid (72JCS(P1)2593), or FeCl₃ (81JHC1161), or from the hydrocarbons with chromic acid (45JA1643; 46JA1456) or by anodic oxidation (79CC1172; 83JOC4312).

Among the cyclization approaches, a one-pot synthesis of the 5-phenylthio derivative of **157** was devised starting from 3-thenoyldiethylamide. This was ortho lithiated and condensed with 3-(phenylthio)acrolein, followed by phenyl sulfide-directed α -lithiation and intramolecular anionic cyclization with air oxidation (85TL6213). The isomeric 5(6)-hydroxy-6(5)-methyl derivatives of **157** were obtained in low yield by condensation of 2,3-diformylthiophene with hydroxyacetone (71BSF1437). There are also syntheses from benzoquinones, with subsequent formation of the thiophene part (71CC73; 72LA28; 76MI6).

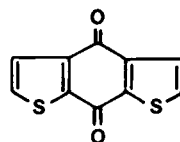
Much more work was done on extended quinones. Syntheses of six parent compounds (**159**–**164**) has been accomplished by two methods. In the first approach, a Friedel–Crafts reaction between thiophene-3,4-dicarboxylic acid and benzene or thiophenes was used, and in the second one chromium trioxide oxidation of the corresponding acetoxy derivatives was applied (72JOC1712). These systems behave differently in the presence of excess lithium aluminum hydride and aluminum hydride. Compounds **161** and **162** were reduced to hydroquinones, compounds **160** and **163** were deoxygenated



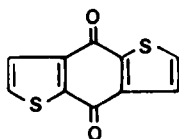
(159)



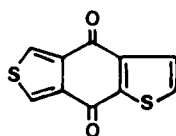
(160)



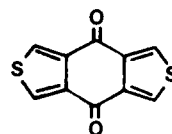
(161)



(162)



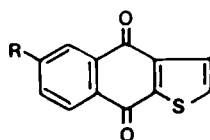
(163)



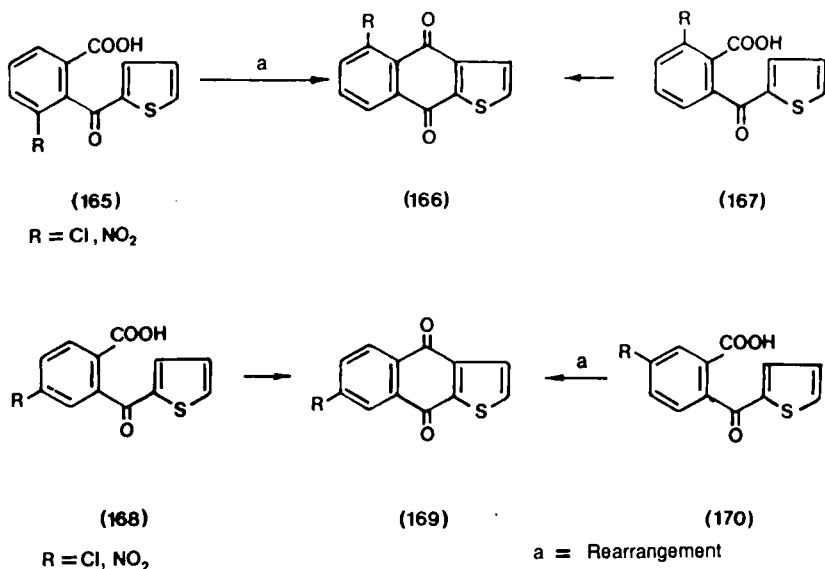
(164)

and reduced to the dihydro derivatives, whereas **159** was transformed into a mixture of the fully aromatic system (40%) and the dihydro derivative (25%) (72JOC1712).

Substituted thienoquinones of type **159** were prepared by ring closure of the corresponding thenoylbenzoic acids. It was found that ring closure of chloro- and nitrothenoylbenzoic acids substituted in the benzene ring proceeds normally when the substituent is in the position meta to the thenoyl group (**167** or **168**). When the substituents are ortho (**165**) or para (**170**), ring closure takes place with rearrangement. The reverse situation was observed when amino groups are present, and normal cyclization takes place if these groups are in the ortho or para position, whereas with meta-substituted precursors, rearrangement takes place (Scheme 1) (52JA4357). It was found that, in concentrated sulfuric acid above 140°C, nitrothenoylbenzoic acids rearrange; from either **168** (R = NO₂) or **170** (R = NO₂), a mixture of about equal amounts of the cyclized products **169** (R = NO₂) and **171** (R = NO₂)

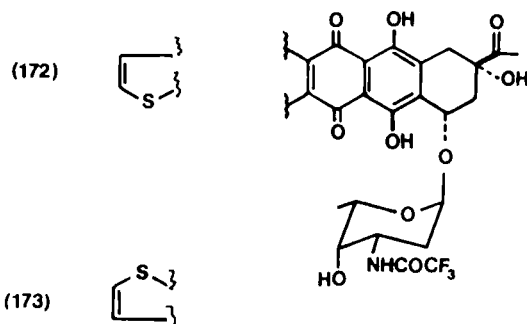


(171)



SCHEME I

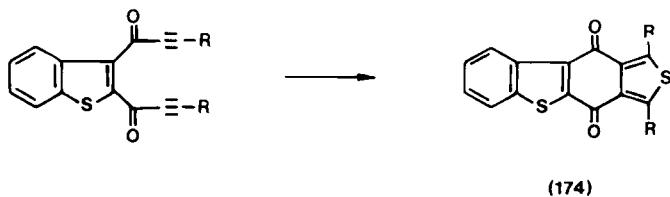
was obtained (58JA3652). Similar observations were made with the analogous naphthoic acids (40JA3098). Cyclizations of this type were used to synthesize the unsubstituted system **159** (15LA94; 52JA4353), its derivatives (52JOC705; 57JCS1525), and some extended systems (31LA259; 45JA1305; 56JCS1429; 60JCS433). The parent **159** was obtained also by chromium trioxide oxidation of the bromo or acetoxy precursors (62JCS704; 63JCS4477), and some extended analogs were prepared from the corresponding heteroaromatics after chromic acid or dichromate oxidation (51PIA(A)85; 52JA4361; 76S675). Compound **159** was obtained also from degradation of an antitumor antibiotic calicheamicin γ_1 (87JA3466).



Thiophene analogs of daunomycin (**172**, **173**) were prepared in multistep reactions. The synthesis is based on a strong base-induced cycloaddition of homophthalic anhydrides. In the final step, glycosidation yielded a mixture of α - and β -glycosides from which the α -isomer was separated (87TL3971).

o-Diketodienes of benzothiophene readily form complexes with rhodium compounds. These complexes reacted with sulfur to give the quinones **174**. With selenium or tellurium they give the corresponding analogues (75CB237).

The isomeric quinones **175**, **176**, and **177** were prepared from the corresponding dithiophene dialdehydes by a benzoin-type condensation and subsequent oxidation by air (69RTC1244).



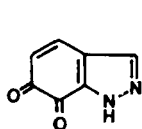
A tetra- and pentacyclic quinone were prepared from thioisatin. Reaction with 2-bromoacetylthiophene yielded the benzo analog of **161**, and from 2-bromoacetylbenzo[*b*]thiophene the dibenzo analog of **162** was obtained in very low yield (53MI2).

IV. Quinones with a Condensed Five-Membered Ring with Two Heteroatoms

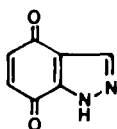
A. PYRAZOLE DERIVATIVES

There are only a few derivatives of the indazole-6,7-dione **178** and 4,5-dione; all other indazolequinones belong to the 4,7-dione system **179**.

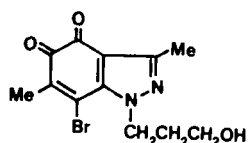
Unsubstituted **178** and some 4-substituted derivatives were prepared by conventional oxidation of the 7-amino-6-hydroxy- or 6,7-dihydroxy- or chlorohydroxyindazoles (12LA318; 14LA81; 26JA1097).



(178)



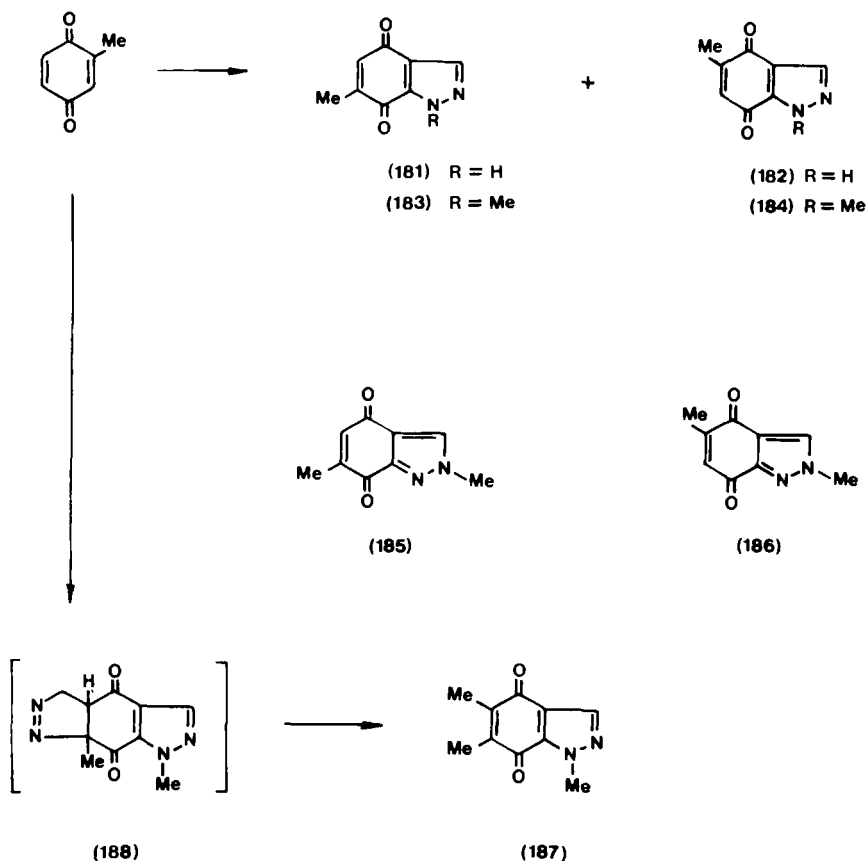
(179)



(180)

Only a few derivatives of **179** were prepared similarly with MnO_2 (77C49, 77ZN(B)1072) or periodic acid (82LA420). A mixture of the 4,7-dione (88%) and the 4,5-dione **180** (11%) was obtained when the 5,7-dibromo-4-hydroxy precursor was oxidized in the same manner (82LA420).

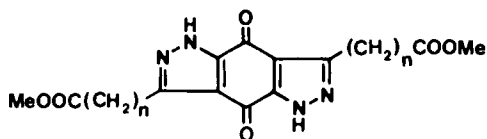
The great majority of the 4,7-diones was prepared by cycloaddition of diazo compounds to quinones. Quinones can react with diazomethane in a different way, i.e., they can react either at the carbonyl group or they can undergo a 1,3-dipolar cycloaddition on the carbon-carbon double bond. In several cases, the nonaromatic cycloadducts were obtained; they are quite stable and do not eliminate other groups that may be present (69CB3111). Aromatization of the cycloadduct can be achieved with FeCl_3 (66MI1; 67CB3413), dibenzoyl peroxide (72CB3915), or other reagents (31JA4080; 35JA1479; 79IZV1807). When excess of the diazo compound is used, additional reactions can take place. As an example, the reaction between 2-methyl-1,4-benzoquinone (*p*-toluquinone) and diazomethane is discussed (Scheme 2). With 1 equivalent of diazomethane, a product was obtained that was assigned structure **181** based on the NMR spectrum. It is a mixture, and previously no clarification of the regioisomers was given (55RTC737; 60M1052; 66MI1). It consists of the 6- (**181**) and 5-methyl (**182**) isomers. Further methylation with diazomethane afforded the corresponding 1-methyl (**183** and **184**) and 2-methyl derivatives (**185** and **186**) of both regioisomers (83JHC1315). With 5 equivalents of diazomethane, the trimethyl derivative (**187**) was obtained in 2% yield, together with **183** and **184**. The reaction is explained as proceeding via the cycloadduct **188**, from which an extra methyl group is generated (83JHC1315).



SCHEME 2

Diazomethane additions to amino- or anilino-1,4-benzoquinones (75CB2941; 81M605) and 2,5- or 2,6-di-*tert*-butyl-1,4-benzoquinone (70LA87) were studied. In the last case, from the adduct one *tert*-butyl group is eliminated under the influence of the acid. In other cases, elimination of a halogen atom or a methylthio group was observed (38JOC125; 62CB2403). 2,3-Dichloro-1,4-benzoquinone reacts similarly (75CB693; 83JMC876). Facile nucleophilic substitution of a chlorine atom is possible and chlorine at position 5 is replaced preferentially (83JMC876). Some substituted indazole-4,5-diones were reported to be active against the growth of certain rodent tumors (74IJC129; 83JMC876).

1,4-Benzoquinone reacts readily with either diazomethane or diazoethane to give a bis adduct (189), which can be further N-alkylated (72CB3915; 75CB693). Instead of diazoalkanes, mesoionic heterocycles may be used.

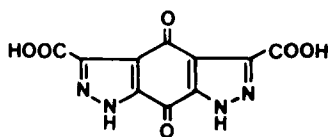


(189)

X-Ray analysis of a 2-phenyl derivative of **179** revealed that the bond lengths and bond angles of the pyrazole part are similar to those reported for an unsubstituted pyrazole ring and that the carbon-carbon and carbon-oxygen bonds in the quinone part are clearly double bonds (87JHC971).

1,4-Naphthoquinones react with diazomethane similarly (35CB1479; 38JOC125; 62CB2403; 63JCS5342; 65TL4593; 67JPR73). 3,7-Dimethyl-1,2-naphthoquinone does not react with diazomethane and 3,7-dimethyl-1,4-naphthoquinone yielded only a dinaphthylmethane derivative (34JA2690).

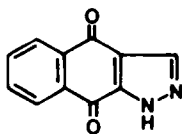
The reaction between quinones and diazo esters with three to six carbon atoms was investigated. Adducts with 1,4-naphthoquinones were isolated and then aromatized. 1,4-Benzoquinone reacted with methyl diazopropionate to give a monoadduct, whereas with other diazo esters bis adducts were formed, for which structure **189** was postulated (67JPR73). 2-Methoxy-1,4-benzoquinone reacts with ethyl diazoacetate to give the indazoloquinone (51JCS2352), but 2,6-dichloro-1,4-benzoquinone underwent addition on both carbon-carbon double bonds and on one carbonyl group. The adduct is transformed upon oxidative hydrolysis into **190** (73CB727).



(190)

Addition of vinyl diazomethane to quinones gave the corresponding vinyl-indazoles or benzo analogs. Their polymerization behavior and properties of redox polymers were investigated (67CB3413; 68CB1987; 71TL2443; 72AG361, 72CPB1785; 73MI1, 73MI2; 74MI1).

An unusual formation of naphtho[2,3-*c*]pyrazole-4,9-diones **191** was observed when actinorhodin, a red pigment from *Streptomyces*, or other bis(1,4-naphthoquinone) derivatives were treated with diazomethane. The reaction involved the formation of a cycloadduct (64CB2555), and thereafter



(191)

the bond linking both naphthalene residues is broken (62CB810, 62N130; 66LA209). A carbon-carbon bond is also broken when the cycloadduct between 5-amino-8-hydroxy-1,4-naphthoquinone and cyclopentadiene reacts with diazomethane to give derivatives of **191** (86T4309). The tricyclic system was prepared also by 1,3-dipolar cycloaddition of a nitrileimine to 1,4-naphthoquinone, whereas the 2-methyl analog gives a cycloadduct but no aromatization takes place (62T3). Glycosidations were studied and a mixture of the N-1 and N-2 glycosides is obtained (77JMC818; 78MI1).

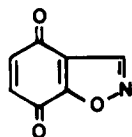
There are few syntheses in which the pyrazole part is formed by cyclization. Derivatives of **179** were obtained from quinones with a keto or carbalkoxy functional group and hydrazines (71AG442; 74IJC129; 76CPB1731, 76IJC(B)575; 84JHC825). In reverse manner, pyrazole-4,5-dialdehyde gave with glyoxal and potassium cyanide and in the presence of base the same system in low yield (43CB818).

Several extended pyrazoloquinones were prepared either as analogs of mitosenes (84LA1711) or from studies of various sydnone and quinones (65JCS5871).

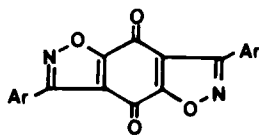
B. ISOXAZOLE AND ISOTHIAZOLE DERIVATIVES

Derivatives of isoxazole-4,7-dione **192** are prepared by cycloaddition of benzonitrile oxides to quinones, followed by aromatization. 2-Methyl-1,4-benzoquinone reacted on both carbon-carbon double bonds, and only the adduct at the C-5—C-6 bond could be aromatized. The 2-methoxy analog gave two regioisomeric adducts, both formed on the unsubstituted side of the quinone, and the 2,6-dimethoxy analog reacted with elimination of the methoxy group to give 6-methoxy-**192**. In the case of 2,5-dichloro-1,4-benzoquinone, addition with dehydrochlorination took place (84BCJ1643, 84BCJ2216). 1,4-Benzoquinone gave the bis adduct, which was formulated as **193** (68G891).

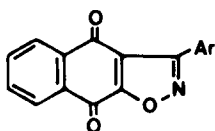
These cycloadditions have been applied also to naphthoquinones (50G140; 68G891; 69G565) to give derivatives of **194** and **195**. Derivatives of **194**



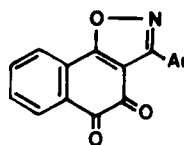
(192)



(193)



(194)



(195)

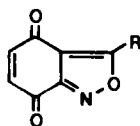
or **195** undergo photochemical N—O bond cleavage to give substituted naphthoquinones (73CC218).

Quinones undergo 1,3-dipolar cycloaddition also with arylhydroxamoyl chlorides to give **194** (68BCJ2206). Another system, **196**, was obtained from 2-acetyl-3-amino- or -anilinoquinones and hydroxylamine or from 2-carbalkoxy-3-chloroquinones and sodium azide or primary and secondary aliphatic amines (67TL4313; 71AG442; 74S30; 76IJC(B)575).

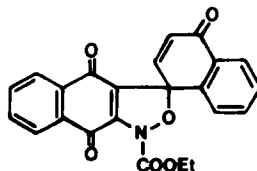
Another variant is oxidative cyclization of 3-amino-2-carbalkoxyquinones with lead tetraacetate (85JHC697). Compounds of the **196** system can be regarded as intramolecular stabilized nitrenes. They react readily with dimethyl sulfoxide by ring opening of the heterocyclic part (85JHC701), but derivatives of **198** were also obtained as by-products (85JHC705).

From thermolysis of ethyl azidoformate with 1,4-naphthoquinone, a mixture of compounds was obtained, among them a product with the probable structure **197** (77CJC2363).

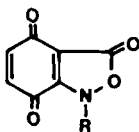
So far, there are only few representatives of the isothiazolo-4,5-dione system **199**, and they were obtained from nitric acid oxidation of the hydroxy precursors (27LA264).



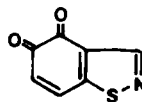
(196)



(197)



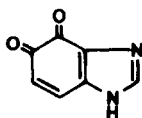
(198)



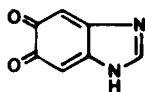
(199)

C. IMIDAZOLE DERIVATIVES

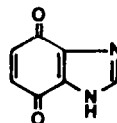
Representatives of the three isomeric benzimidazolequinones **200**, **201**, and **202** are known. The majority of these compounds was prepared by oxidation of the corresponding hydroxy, amino, dihydroxy, dimethoxy, or amino-hydroxy precursors. Derivatives of **201** were prepared with Ag_2O , FeCl_3 , or nitric acid (60ZOB3319; 70JHC39, 70JHC249) and those of **200** with nitric acid as oxidant (27LA225; 64ZOB3738).



(200)



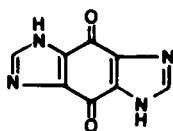
(201)



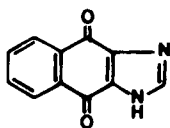
(202)

Compounds related to **202** were obtained using Ag_2O (70JHC39, 70JHC249), FeCl_3 (53ZOB951; 63ZOB3965; 64ZOB197; 66ZOR1095; 70JHC249; 82H2313; 86JOC522), nitric acid (27LA225), dichromate, or chromic acid (59JOC1451; 66ZOR1095) as oxidants. Benzimidazoles can also be directly converted into the quinones **202** or **203** with dichromate, chromic acid (35LA248; 52ZOB1015), CAN (76JHC1121), or FeCl_3 (53ZOB951). Compounds related to **203** were also prepared from the dihydroxy precursors and chromium trioxide (61HCA762).

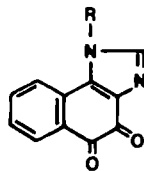
Numerous derivatives of **204** were synthesized from 2-amino-3-acylaminonaphthoquinones by base-induced cyclization (25CB1128; 54JA4148; 60JOC753, 60ZOB2670; 64JMC362; 65ZOR1458). In an analogous manner, the angular system **205** was obtained from 1,2-quinones (1898CB2405; 38HCA56). The aminoquinones can also be used as starting material, and from tetraamino-1,4-benzoquinone and aliphatic aldehydes compounds of the type **203** were obtained (37LA38; 69T2427). In an analogous manner, derivatives of **204** were prepared from 2,3-diamino-1,4-naphthoquinone with either acetylacetone, urea, or diethylcarbamoyl chloride (65ZOR1117; 67ZOR162).



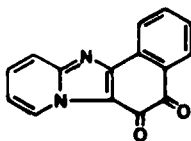
(203)



(204)



(205)



(206)

Tetracyclic quinone **206** was obtained from 2,3-dichloro-1,4-naphthoquinone and 2-aminopyridine in an unexpected manner (63JOC1019).

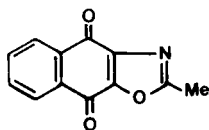
Investigations regarding the reactivity of these systems include N-methylation, the introduction and substitution of various functional groups at position 2 (67ZOR575), glycosylation (77JMC818), studies of anion radicals (73JMR331), spin density distribution (73JMR229), reduction potentials (27JA2604), and xanthine oxidase inhibition (86B4189).

Reaction of dibromo-**202** with ethyl acetoacetate and pyridine gave a tetracyclic quinone (70JHC395), and Diels–Alder reaction transformed **202** into the extended quinones (70JHC425).

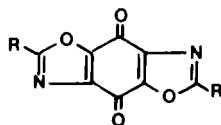
D. OXAZOLE AND THIAZOLE DERIVATIVES

Only a few oxazoloquinones are known. 2-Methylnaphtho[2,3-*d*]oxazole-4,9-dione (**207**) was obtained from 2-acylamino-3-alkylamino-1,4-naphthoquinone in the presence of concentrated sulfuric acid (69T2427). Similarly, derivatives of **208** were obtained from 2,5-bis(acetylamino)-3,6-dihydroxy-1,4-benzoquinones and acyl halide or anhydride (64ZOB3037). The five-membered ring is easily cleaved in warm dilute acid or base (64ZOB3037).

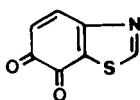
Thiazolequinones **209** were prepared from the corresponding 6-hydroxy precursors by oxidation with nitric acid (27LA233) or with oxygen in the presence of copper acetate and a secondary amine. They were transformed in an acid-catalyzed isomerization into 6-hydroxy derivatives of **210** (71KGS196, 71M13). Oxidation of the dihydroxy or diamino precursors is the exclusive method for the synthesis of **210** derivatives (37LA38; 53UKZ508; 73JMC1314). Nitric acid oxidation of the hydroxytrichloro precursor afforded the isomeric quinone **211** (37LA60).



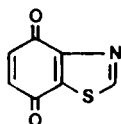
(207)



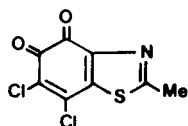
(208)



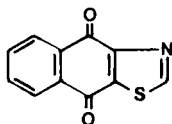
(209)



(210)



(211)



(212)

The extended quinone **212** was obtained from 2-amino-3-mercapto-1,4-naphthoquinone, prepared *in situ*, and formaldehyde, with dehydrogenation taking place simultaneously (50JCS680). All attempts to reduce the quinone were unsuccessful.

The 6-hydroxy-5-*n*-undecyl derivative of **210** (UHDBT) is a structural analog of ubiquinone. It inhibits the oxidation of succinate and NADH (78MI2; 85MI3), blocks the respiratory chain in membranes from *Pseudomonas cichorii* or *Pseudomonas aptata* (85MI4), and increases the activity of cytochrome c_1 about 2-fold (86MI5). It also inhibits the conversion of *p*-hydroxybenzoic acid (77BBR1536).

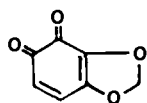
E. 1,3-DIOXOLANE AND 1,3-DITHIOLANE DERIVATIVES

There are three isomeric parent systems: **213**, **214**, and **215**. Compounds belonging to **213** seem not to be described.

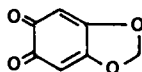
From the basidiomycete *Phlebia strigosozonata*, a red pigment was isolated, phlebiarubrone, for which evidence as a 4,7-diphenyl derivative of **214** has been forwarded (63TL335; 67T3985). Other derivatives of this system were prepared from the corresponding dimethoxy precursors with dilute nitric acid (72CB614).

Representatives of the **215** system were obtained from phenolic precursors and Fremy's salt or CAN (79ZN(B)624; 83ZN(B)392). They undergo a

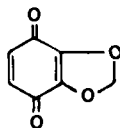
Diels–Alder reaction to give benzo analogs of **215** (83ZN(B)392), which were also obtained by bromine oxidation of the polycyclic precursors (86CZ455). Quinone **216** was prepared with diazomethane (83ZN(B)392).



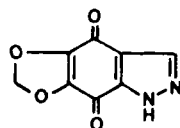
(213)



(214)



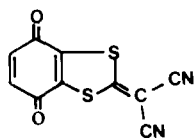
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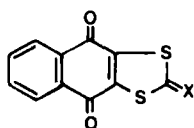
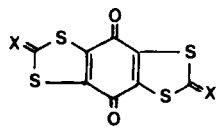
(216)

Quinones with a sulfur-containing annelated ring are strong electron acceptors and some of their charge transfer complexes with electron donors show high electrical conductivity (86CC1489).

Dithioacetic acid derivatives add to 1,4-benzo- or 1,4-naphthoquinones to give, after oxidation of the adduct with silver oxide or chloranil, the quinones **217** and **218** (69LA103). Quinones **218** were prepared also from 2,3-dichloro-1,4-naphthoquinone and salts of dithiocarbamic acids (51JA3459) and those of type **219** by oxidation of the corresponding hydroquinones. From reduction potentials and the semiquinone formation constants, it was concluded that their anion radicals are thermodynamically stable (86CC1489).



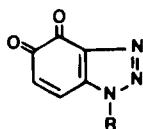
(217)

(218) $X = C(CN)_2$,
S, O, NR(219) $X = C(CN)_2$,
O, S

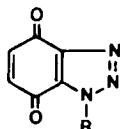
V. Quinones with a Condensed Five-Membered Ring with Three Heteroatoms

A. TRIAZOLE DERIVATIVES

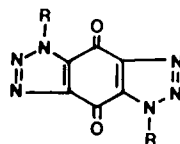
The usual methods of phenol oxidation were used to prepare derivatives of **220** (or the tautomeric form of the triazole part) (12LA318; 12LA345; 27LA131; 34LA213; 34LA241) or of **221** and benzologs (35LA248). When 1-amino-4,7-dimethoxybenzotriazole was demethylated with boron tribromide and the resulting quinol oxidized with silver oxide, the unstable 1-amino derivative of **221** was obtained. Although it rapidly decomposes, it was identified by the formation of a cycloadduct, resulting from the decom-



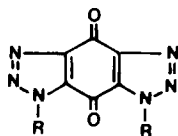
(220)



(221)



(222)



(223)

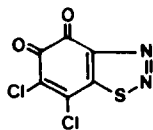
position product, the "benzynequinone" (69CC647; 70JCS(C)583). Quinone **222** and its N-substituted derivatives were obtained by dichromate oxidation of the parent heterocycle (58CLY486; 75JHC235).

A simple synthesis uses addition of azides to quinones. 1,4-Benzoquinone adds phenyl or methyl azide to give little monoadduct but more of the two isomeric bistriazolo derivatives **222** and **223** (12LA68; 35JA1479). 1,4-Naphthoquinone reacts similarly and at higher temperatures the adduct loses nitrogen and undergoes ring contraction to give a 1,3-indandione derivative (13LA274). Addition of glycosyl azides at room temperature for 50 days afforded the N-glycosyl derivatives (78MI1). These were obtained also by direct ribosylation (77JMC818).

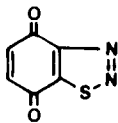
Substituted **222** or benzologs of **221** were prepared from 2,3-diaminoquinones and nitrous acid (25CB1128; 35JA1844; 65JCS2727). Alternatively, 1,2,3-triazole-4,5-dialdehydes and glyoxal form the 5,6-dihydroxy derivative of **221** (43CB818). Triazolequinones with an additional oxygen, sulfur, selenium, and nitrogen atom in the five-membered ring were prepared from *o*-diketodiyne of 1-phenyl-1,2,3-triazole (74LA1876). Electron spin resonance (ESR) spectra of quinones such as **223** were recorded (78JCS(F2)2027).

B. THIADIAZOLE DERIVATIVES

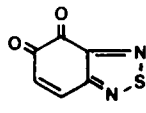
Compounds belonging to systems **224**, **225**, **226**, and **227** are known. Compound **224** was prepared from the phenolic precursor with nitric acid (27LA172); dichromate oxidation of the dihydroxy precursor yielded **225** (37LA38). Quinone **226** was obtained from the 4-chloro- or -bromo-5-hydroxy



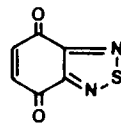
(224)



(225)



(226)



(227)

precursor with nitric acid (87KGS850). Similarly, 4-hydroxy-, 4-amino-, 4-amino-7-hydroxy-, or 4,7-diaminobenzo-2,1,3-thiadiazoles were transformed with dichromate into the quinone **227** in various yields (73KGS926; 78KFZ66). The benzo analogue of **227** was prepared from 2,3-diamino-1,4-naphthoquinone and thionyl chloride (57CB1137).

VI. Quinones with a Condensed Six-Membered Ring

A. AZAQUINONES

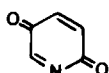
Theoretically, three azaquinones (**228**–**230**) are possible. Compound **230** was postulated as the oxidation product of 2,5-dihoxypyridine (1897M613), but that compound was later found to be a dimer (**231**) (65CB2139). Oxidation of either 3-amino-2-pyridone or 5-amino-2-pyridone, preferably with potassium bromate, gave a product for which an equilibrium between the 6-hydroxy derivative of **228** and the 3-hydroxy derivative of **230** was postulated



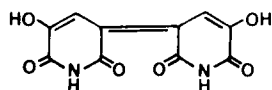
(228)



(229)



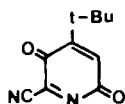
(230)



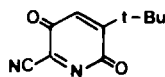
(231)

(57JA3552). Upon reductive acetylation, 2,3,6-triacetoxypyridine is obtained. The quinone is rapidly decomposed in alkaline solution and in the presence of oxygen with evolution of ammonia. Interestingly, the 3- or 5-methyl analog formed a monophenylhydrazone. Another related compound is the 3-phenyl-4-methyl analog, prepared by hydrolysis of 2-nitroso-3,6-dihydroxy-4-methyl-3-phenylpyridine (59JA6049). So far, there is no evidence for which of the hydroxy-substituted azaquinone forms is predominant (57JA3552; 59JA6049; 73AG163).

From the thermal rearrangement of 5-*tert*-butyl-2,3-diazido-1,4-benzoquinone, almost equal amounts of the azaquinones **232** and **233** were obtained



(232)



(233)

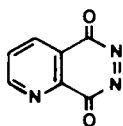
(75JA6181). Thermal rearrangement of diazidoquinones to 2-aza-3-cyanoquinones opened a new, general route to azaquinones and the reaction was elaborated also in the naphthoquinone series to give isoquinoline-1,4-diones (75JA6181).

Quinoline-3,4-dione is an impure yellow powder (31G959) and its 2-hydroxy-7-methyl analog (or tautomer) was obtained from 7-methylquinoline-2-one by oxidation with chromic acid. With alkali it is decomposed to 4-methylbenzoic acid (48CB483).

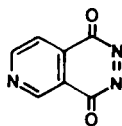
In some cases azaquinones were isolated as cycloadducts with dienes (75JA6181). They have an electron-deficient imine double bond, to which a variety of nucleophiles, and *m*-xylene, nitromethane, and enamines, add (69HCA1810). Azaquinones are potent dienophiles.

3-Phenylisoquinoline-1,4-dione was prepared in several ways. It is obtained either from pyrolysis of 2-azido-2-phenyl-1,3-indanedione (71TL1621). Alternatively, upon heating *in vacuo*, the 3-phenyl-3-acetoxy precursor eliminates acetic acid (68HCA413; 69HCA1810). The azaquinone is a red, very reactive compound. It is readily hydrated in moist air, undergoes cycloadditions, and adds even *m*-xylene, but not toluene (69HCA1810; 71TL1621).

The isomeric pyridopyridazinediones were oxidized with lead tetraacetate to give the unstable quinones **234** and **235**, which were trapped with cyclopentadiene (73JCS(P1)26).



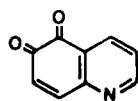
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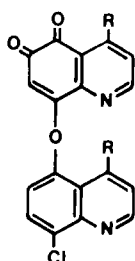
(235)

B. QUINOLINE DERIVATIVES

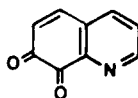
Few derivatives of quinoline-5,6-dione (**236**) are known. They were prepared from the corresponding hydroxy or dihydroxyquinolines by oxidation with air or oxygen (51JA544; 67MI1, 67MI2; 70KGS1376; 73KGS1700), chromic acid, or lead tetraacetate (54JA2400). Oxidation with Fremy's salt



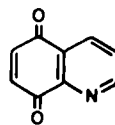
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(237)



(238)



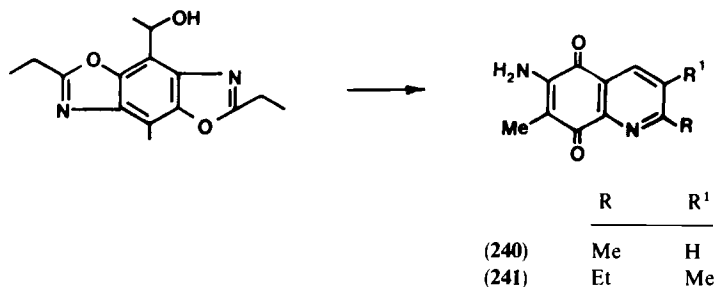
(239)

was also successful, but 8-chloro-4-hydroxyquinolines formed ethers **237** (67CB2918). The 8-morpholino derivative of **236** reacts with ethylenediamine to form a new pyrazine ring (86KGS959). Compound **236** and derivatives can be isomerized to the *p*-quinonoid system **239** in the presence of sodium hydroxide (70KGS1376).

There are also a few compounds belonging to the 7,8-dione system **238**. 8-unsubstituted 7-hydroxyquinolines are oxidized with Fremy's salt to **238**. Because the formation of these quinones is slow, other reactions can take place. In acid solution, dimeric compounds are formed and, in neutral solution, ethers similar to those in the 5,6-dione series (**237**) are formed (67CB2077).

Most investigations in the quinoline series are related to quinoline-5,8-dione system **239**. The parent quinone was obtained first in 1884 by dichromate oxidation of 8-hydroxy-5-aminoquinoline (1884CB1642). Almost all other derivatives were prepared thereafter by oxidation of 5- or 8-hydroxy- or aminoquinolines, or 5,8-dihydroxy-, 5,8-diamino-, or aminohydroxyquinolines with Fremy's salt (54CB1236; 75JHC725), dichromate (41JA1470; 53JCS3161, 53RC390; 54JCS570; 60JA1155, 60MI1; 61G926; 68JOC1089; 74JHC519), FeCl_3 (57JA5024), lead tetraacetate (73JCS(P1)26), oxygen (65MI3), oxidative chlorination with simultaneous introduction of chlorine atoms at positions 6 and 7 (53RC390; 86JMC1329), or nitric acid (75JHC725). A number of 4-hydroxyquinoline-5,8-diones were prepared from the corresponding hydroxyquinolines with Fremy's salt, FeCl_3 , or sometimes advantageously with CAN (54LA75; 60CB642; 61G926; 69KGS682, 69KGS687, 69KGS690; 73JCS(P1)2374).

There are also some special syntheses. For example, in an attempted acid-catalyzed hydrolysis of a benzobis(oxazole) into a diaminobenzoquinoline-quinone, **240** was obtained instead. This compound has two more carbon atoms than expected. In addition, in the presence of acetaldehyde, the yield of **240** increased whereas addition of propionaldehyde generated compound **241**. During these transformation, 2 equivalents of the aldehyde are incorporated in what is explained as a retroaldol reaction of benzobis(oxazole) during deprotection (85JOC4276).



Another approach is a palladium-catalyzed cyclization. 2-Allyl-3,6-diamino-5-methyl-1,4-benzoquinone was transformed into the 5-amino-6-methyl analog of **289** (85JOC4276). Oxidative cyclization with chloranil was also effective.

In addition to the normal reactivity of quinones, some particular transformations of **239** and derivatives are worth mentioning. Quinoline-5,8-diones are aminated with aromatic amines to give 6-amino derivatives as the main products, and 7-amino compounds as minor products (62JOC3905). In the presence of cerium ions only 6-amino derivatives are formed and yields are greatly improved. Similarly, 6- or 7-halo-substituted compounds are aminated in the presence of cerium ion at position 6, regardless of whether this position is free or substituted. A theoretical explanation for these effects has been given (62JOC3905). With *N,N*-dialkylanilines in the presence of metal ions, 6-arylated products are formed selectively. *N*-Alkylanilines give a mixture of the arylated and aminated products (87CL1191).

6-Methoxyquinoline-5,8-diones can be regarded as vinylogs of an ester and they react with primary or secondary amines to give 6-amino derivatives (55JA37; 74JHC519). The 6-hydroxy analog can be alkylated at position 7 with diacyl peroxides. When subjected to Hooker oxidation (36JA1163), the corresponding 6-alkyl-7-hydroxy analogs with one fewer carbon atom in the alkyl chain are formed (55JA4664).

Quinone **239** adds hydrogen chloride to give the 6-chloro compound after subsequent oxidation; the 7-chloro isomer is obtained as a by-product (87OPP249). Reactions with pyridine have been described (58MI3; 71JMC1029). With dienes, adducts are formed that can be isomerized with acid into hydroquinones, which can be reoxidized with silver oxide to quinones (67JHC133; 73JCS(P1)2374).

6,7-Dichloroquinoline-5,8-dione is converted by peroxytrifluoroacetic acid into the *N*-oxide in low yield. This compound is also obtainable directly from 8-hydroxyquinoline with a mixture of concentrated hydrochloric and nitric acids (86JMC1329). The 6,7-dichloroquinone reacts also with imidazole to give the disubstituted product (72LA131).

^{13}C -NMR spectra of many quinoline-5,8- and -5,6-diones were reported (85CPB823). Biological activity of some quinolinediones has been reported (59N82; 73JMC206), and classification studies with pattern recognition methods (80JMC595) and correlations of electronic properties and anti-malarial activity were also presented (73JMC1089).

C. STREPTONIGRIN AND LAVENDAMYCIN

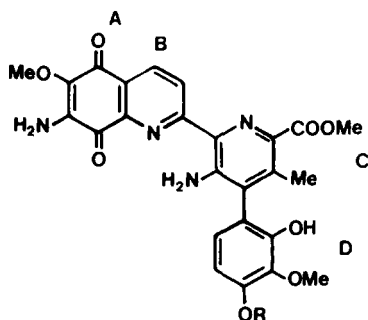
Certain quinones exhibit high anticancer activity. Among them are mitomycins and streptonigrin. Streptonigrin (**242**, $\text{R} = \text{Me}$) is a metabolite of few species of *Streptomyces* and actinomycetes. It is effective against a variety of human tumors, but its high toxicity precluded its clinical use (for recent review and earlier references, see 77H1485; and 82MI1). From *Streptomyces albus*, an analog, desmethylstreptonigrin (**242**, $\text{R} = \text{H}$), was isolated (86MI7) and it is also an antitumor antibiotic.

Structurally and biosynthetically related to streptonigrin is lavendamyacin (**243**), isolated from *Streptomyces lavendulae* (82MI5). In addition to these antibiotics, a new metabolite was isolated from *Streptomyces* species, streptonigrin (**244**). It is a pyridone derivative with no antimicrobial activity (85MI5).

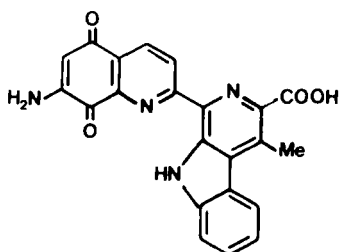
There has been considerable research concerning synthesis of these compounds and analogs, their mechanism of action, and the elucidation of their biosynthesis. The first total synthesis of streptonigrin was described in 1980. The strategy followed first the formation of the C–D part (imino Diels–Alder cycloaddition) and in the final stages the A–B part was synthesized (a modified Friedländer synthesis for annulation). The total synthesis involved over 30 steps with an overall yield of 0.013% (80JA3962). An earlier synthetic approach (78TL4775) was later developed into a total synthesis of 23 steps (81JA1271). In the 19 new steps the overall yield was 1.3% and for the remaining 4 steps it was already reported that they proceed with 10% yield (78JOC121).

Another synthetic approach for streptonigrin is based on two consecutive inverse electron demand cycloadditions. In the first one the A–B–C ring system was formed from a 1,2,4,5-tetrazine and the C–D part was constructed from a 1,2,4-triazine (83JOC621; 85JA5745). Another novel total syntheses has also been reported (82JA536).

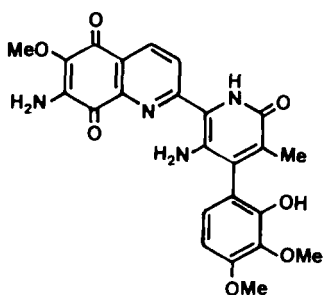
After structural elucidation of lavendamyacin (81TL4595), the proposed structure (**243**) was confirmed by total synthesis of its methyl ester (84H91, 84TL923; 85H261). Another total synthesis of its methyl ester was based on the Friedländer condensation for the A–B part, and this part was connected with a β -carboline moiety (85JOC5790). Moreover, several syntheses of



(242) R = Me, H



(243)



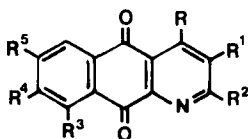
(244)

related compounds like desmethyllavendamycin or its methyl ester have been developed (83H1957; 84IJC(B)496). Also a multistep, regiospecific synthesis of lavendamycin from 8-hydroxyquinoline and indole is described (86T5065). The last step followed a previously described procedure (84TL923). An improved approach for the A-B part of streptonigrin and lavendamycin has been published (86H1067).

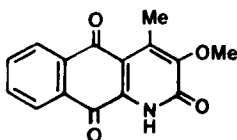
Streptonigrin has been modified insofar as many amide derivatives were prepared by the classical Schotten-Baumann procedure or by a novel one, using 3,3'-(phenylphosphoryl)bis(1,3-thiazolidine-2-thione) (PPBTT) as condensing agent (86JCS(P1)479). For streptonigrin, several biosynthetic pathways have been suggested. In one report (87JA620), 4-aminoanthranilic and 7-aminoquinoline-2-carboxylic acids were shown to be intermediates and ring oxygenation occurred at a latter stage.

D. EXTENDED SYSTEMS

There are some tricyclic quinones isolated from natural sources. Cleistopholine (**245**) is an alkaloid with an azanthraquinone skeleton and was isolated from the root bark (30 mg from 500 g of the bark) of *Cleistopholis patens* from Ghana. The structure was established on the basis of spectroscopic data (85P523). Of similar structure is dielsiquinone (**246**), one of the eight alkaloids isolated from the trunkwood of *Guatteria dielsiana* (86P1691). For phomazarin (**247**) from *Pyrenochaeta terrestris*, which was isolated in 1944 (40RTC1180), a structure was proposed (44RTC251; 45RTC23). It was reexamined and slightly revised (64TL1853), and then amended to **247** (79JCS(P1)807).

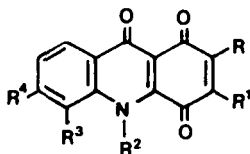


- (**245**) $R^1, R^2, R^3, R^4, R^5 = H, R = Me$
 (**247**) $R, R^1, R^3 = OH, R^2 = COOH,$
 $R^4 = OMe, R^5 = n-Bu$

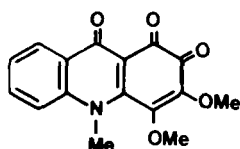
(**246**)

From Australian rutaceae, *Melicope tereana*, several alkaloids were isolated. From melicopine and melicopidine, after demethylation and nitric acid oxidation, two quinones, **248** and **249**, were obtained (49MI1). Melicopine is similarly transformed into both quinones. Chemical degradation of actinomycin yielded a peptide-free quinone, actinomycinol (**250**). The mechanism of conversion of the phenoxazine skeleton in actinomycin into the acridonequinone has been outlined (58JCS469). The compound was synthesized and several derivatives were prepared (56CB1397; 57CB44; 58JCS496).

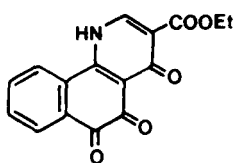
Quinones with the **245** skeleton were synthesized from quinoline-5,8-dione by cycloaddition (64JCS2941; 86JOC2011; 87JOC2285), by Friedel-Crafts reaction between pyridine-2,3-dicarboxylic acid anhydride and hydroquinone



	R	R ¹	R ²	R ³	R ⁴
(248)	OMe	OMe	Me	H	H
(250)	OH	Me	H	OH	Me



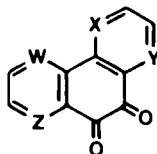
(249)



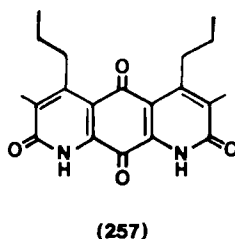
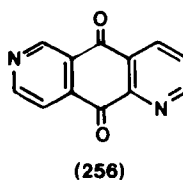
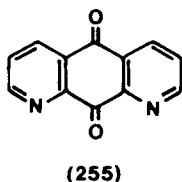
(251)

(29CB509), or by condensation of 2-amino-1,4-naphthoquinone with diethyl ethoxymethylenemalonate or acetylenedicarboxylate, with subsequent cyclization (67JOC3210; 85SC1181). From 4-amino-1,2-naphthoquinone, the angular quinone **251** was obtained (67JOC3210). The parent quinone (desmethyl **245**) was obtained from 3-benzoyl-2-carboxypyridine in sulfuric acid at 270°C (1894CB1925). The standard oxidation of phenolic precursors was also applied (65JCS6074).

Nitric acid oxidation of the corresponding monomethoxy precursors yielded three isomeric phenanthrolinequinones, **252–254** (50HCA1080). The linear analogs **255** and **256** were prepared by cycloaddition of 1-(dimethyl-amino)-3-methyl-1-azabuta-1,3-diene to the corresponding bicyclic quinones (87JOC2285).

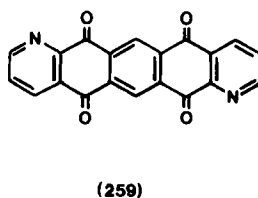
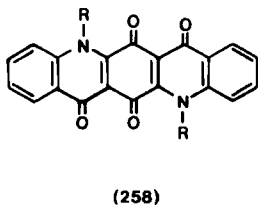


	X	Y	Z	W
(252)	N	CH	N	CH
(253)	CH	N	N	CH
(254)	N	CH	CH	N



Diazaquinomycin A (**257**) is produced by a *Streptomyces* species and exhibits antibacterial activity. It is also an antimetabolite of folate metabolism in *Streptococcus faecium*. Its structural analogs were synthesized (83TL3643).

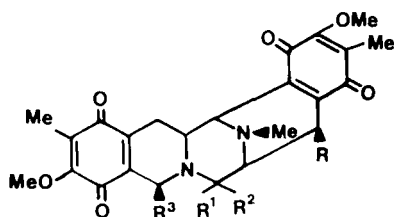
There are a few tetra- and pentacyclic analogues. Benzo analogues of **245** were prepared from pyridine-2,3-dicarboxylic acid anhydride and a tetralin derivative under conditions of the Friedel–Crafts reaction (85JCR(S)338). Pentacyclic compounds **258** ($R = H$ or Me) were prepared from the bis adduct of anthranilic (or *N*-methylantranilic) acid to 1,4-benzoquinone, followed by cyclization in concentrated sulfuric acid (55JCS4440; 66CB1991). 6-Methylquinoline-5,8-dione dimerized in the presence of ethanolic *N*-methylcyclohexylamine to **259** in very low yield and the dimerization is interpreted as two base-catalyzed addition reactions and three oxidation steps (71JCS(C)1253).







E. ISOQUINOLINE DERIVATIVES

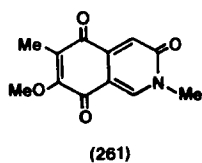
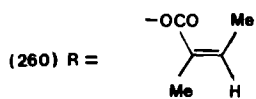
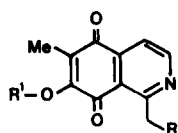
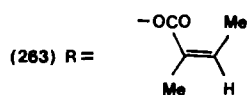
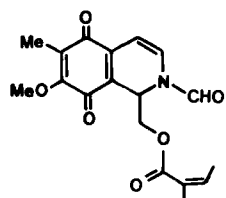
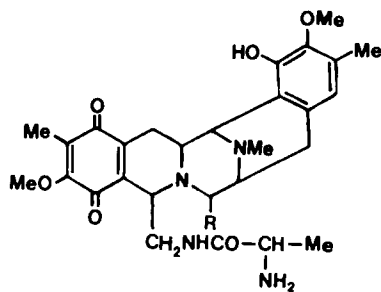
Several isoquinolinequinones are natural products. From a bright-blue marine sponge of *Reniera* sp., renierone (**260**) was isolated as the major antimicrobial antimetabolite (79TL4163). Later, related quinones were isolated

from the same sponge and characterized. These are mimosamycin (**261**) (76MI3; 76MI4), *N*-formyl-1,2-dihydrorenierone (**262**) (82JA265), *O*-demethylrenierone (**263**), 1,6-dimethyl-7-methoxyisoquinoline-5,8-dione, and four related renieramycins, A, B, C, and D (**264–267**). These are dimeric metabolites and are present in minute amounts (compound **267** 0.001%). Also isolated from *S. lavendulae*, in addition to mimosamycin (77TL3825), saframycin A, B, and C (77MI2; 78CPB2175; 79TL2355) was another metabolite, mimocin (**268**) (80TL3207). A characteristic feature of the major antibiotics saframycin A (**269**), B (**270**), and C (**271**), is a dimeric structure of mimosamycin. Structures of mimosamycin (77TL3825; 78AX(B)2899) and saframycin C and B were established by X-ray analysis (79TL2355). Later, new saframycins Y3 (**272**), Yd-1 (**273**), Yd-2 (**274**), Ad-1 (**275**), Y2b, and Y2b-d were isolated (86MI8). Moreover, two antitumor antibiotics, safracin A (**276**) and safracin B (**277**), were isolated from culture broth of *Pseudomonas fluorescens* (83MI3). They are related to saframycins and contain an L-alanylamide side chain in place of a pyruvamide side chain in saframycins.



	R	R ¹	R ²	R ³
(264)	OH	H	H	—OCO— 
(265)	OEt	H	H	—OCO— 
(266)	OH		O	—OCO— 
(267)	OEt		O	—OCO— 
(269)	H	H	CN	—NH—COCOMe
(270)	H	H	H	—NH—COCOMe
(271)	OMe	H	H	—NH—COCOMe

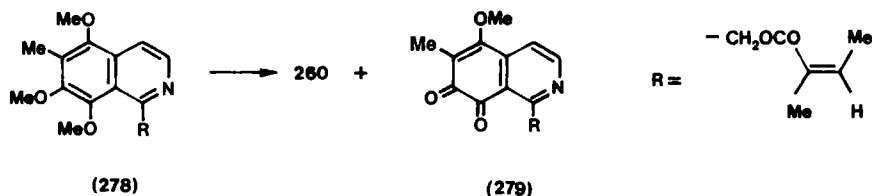
	R	R ¹	R ²	R ³
(272)	H	H	CN	$-\text{CH}_2\text{NHCO}-\text{CH} \begin{matrix} \text{NH}_2 \\ \text{Me} \end{matrix}$
(273)	H	H	CN	$-\text{CH}_2\text{NHCOCH} \begin{matrix} \text{NH}_2 \\ \text{Et} \end{matrix}$
(274)	H	H	CN	$-\text{CH}_2\text{NHCOCOEt}$
(275)	H	H	CN	$-\text{CH}_2\text{NHCOCH}_2\text{NH}_2$

R¹ = MeR¹ = H

(276) R = H

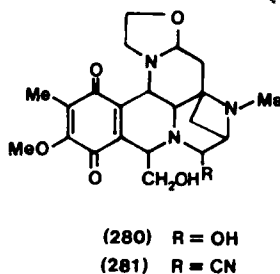
(277) R = OH

Renierone was synthesized from 7-methoxy-6-methylisoquinoline in seven steps (81CPB595; 86CPB4056); **261** and **262** were prepared by the same approach (85CPB2582; 86CPB4056). In another total synthesis, in the last step, oxidative demethylation of **278** yielded a mixture of renierone (**260**) and the *o*-quinone **279** in a ratio of about 3:2 (80TL4819).



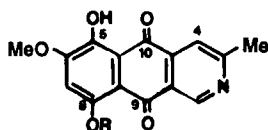
Several syntheses of mimosamycin (77TL3825; 78CPB2175; 87SC657), its 6-desmethyl analogue (78JHC569), and mimocin (80TL3207; 82CL1339, 82CPB4170; 83CPB341), as well as a stereo-controlled total synthesis of racemic saframycin B, from 2,4-dimethoxy-3-methyl-benzaldehyde have been achieved (82JA4957).

Naphthyridinomycin (**280**) and the related congener cyanocycline A (**281**) are antitumor antibiotics (74TL4021; 76AX(B)1139; 82MI7). The structure of **281** was elucidated by X-ray analysis (82MI7). Several approaches



toward the synthesis of naphthyridinomycin have been described (85TL1907, 85TL1911; 86TL6173). Because this antitumor antibiotic is toxic, several syntheses of the less toxic and more stable cyanocycline A have been developed (82MI6; 86JA2478; 87JA1587). A biosynthesis of naphthyridinomycin has also been described (82JA4969).

From *Fusarium oxysporum*, seven quinones were isolated and one of them, 8-*O*-methylbostrycoidin (**282**), was also found in *Fusarium monilliforme*



(282) R = Me

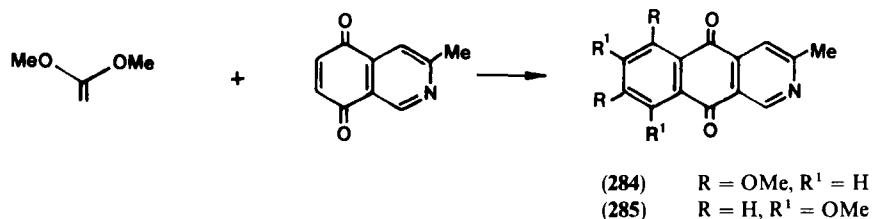
(283) R = H

cultures (79T1551). The structure was determined from chemical and spectroscopic evidence (85P457). Bostrycoidin (283) was isolated from *Fusarium bostrycoides* or *Fusarium solani* (65TL4033). Both compounds have antibiotic properties.

An interesting synthesis was developed for bostrycoidin (283) and its 8-*O*-methyl derivative (282). From 1,2-addition of 1,1-dimethoxyethene to 3-methylisoquinoline-5,8-dione, a mixture (7:1) of the regioisomers 284 and 285 was obtained. The latter could also be prepared in a Minisci-type reaction with subsequent ring closure. After photochemical hydroxylation and demethylation with BCl_3 , 283 was obtained (80TL5089; 82AJC1439).

In general, syntheses of isoquinoline-7,8- or -5,8-diones follow standard methods. Oxidations of the hydroxy or amino precursors are most common. Fremy's salt (85CPB823), FeCl_3 (86SC1557), chromic acid, potassium ferricyanide (62CB2176; 69JHC697), Ag_2O (64JMC801), or oxygen in the presence of copper acetate and a secondary amine (74KGS1253) were used as oxidants. CAN was used for oxidative demethylation of the corresponding methyl ethers. Whereas transformation of 5,8-dimethoxy compounds into 5,8-diones is unambiguous, trimethoxy precursors should, in principle, give both the *o*- and *p*-isomer. It is interesting that if a mixture is formed, the *p*-dione always prevails (83CPB341). Oxidative chlorination was used for the synthesis of 6,7-dichloroisoquinoline-5,8-dione (86JMC1329). On the other hand, isoquinoline-5,6- or -7,8-diones isomerize in the presence of base or acid into the -5,8-diones (74KGS1253; 78CPB2175).

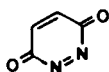
Isoquinoline-5,8-diones undergo Diels-Alder cycloaddition to give derivatives of the linear system similar to 283 (69JHC697). Cycloaddition between 1,4-naphthoquinone and 1-dimethylamino-3-methyl-2-azabutadiene gives cycloadducts in moderate yield (75JA4409; 82TL3261).



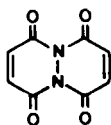
^{13}C -NMR spectra of several isoquinoline-5,8- and -7,8-diones were recorded (85CPB823). A comparative study of electrochemical reduction of isoquinoline-5,8-dione and other heterocyclic quinones revealed that all compounds show two well-defined reduction peaks and that these reductions are reversible (72MI2).

F. PYRIDAZINE DERIVATIVES

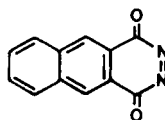
Most research has been devoted to the diazaquinones **286** and their benzologs. Such compounds were prepared from the corresponding pyridazine-3,6-diones after oxidation with either *tert*-butyl hypochlorite or lead tetraacetate at low temperature. This methodology was used to prepare the parent compound **286**, and its 4,5-difluoro and benzo analog (60JOC1724; 62JA966). They are very reactive compounds and the parent dione was not isolated. They decompose by losing nitrogen and from **286** the bicyclic compound **287** is formed. In a similar manner, the benzolog of **286** was characterized by interception with butadiene and, after nitrogen elimination, the dibenzo analog of **287** was obtained (62JA966). All diazaquinones readily add nucleophiles at the carbonyl group. Hydrolysis, chemoluminescence, and electronic spectra of these compounds were studied (86JA7716).



(286)



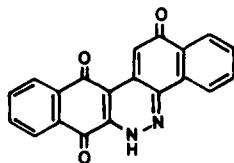
(287)



(288)

Compound **288** was prepared by chlorine oxidation of the monosodium salt of the cyclic hydrazide at -50°C . It rapidly formed a Diels-Alder adduct, but is stable at -20°C for months in contrast to other diazaquinones (68JA5932).

6,7-Dichlorophthalazine-5,8-dione was obtained in low yield by oxidative chlorination of 5-aminophthalazine (86JMC1329). 1,4-Naphthoquinone reacts with hydrazine to give a black compound, for which the structure of a pentacyclic quinone (**289**) was established (67T2911). The compound is identical with the product from treatment of binaphthoquinone with hydrazine and for which a hydrazone structure was postulated previously (39CB1623).



(289)

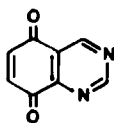
G. PYRIMIDINE DERIVATIVES

With few exceptions, only quinazoline-5,8-dione, its derivatives, and benzologs are known. The major synthetic approach for these compounds is the oxidative formation of the quinone moiety. 5,8-Dihydroxyquinazoline is oxidized with dichromate to **290**, which is stable under normal conditions (70JMC161). Various derivatives of **290** were prepared similarly (70JMC161; 71AG442; 72KGS841; 74KGS1559; 75IJC1009; 76LA1809; 83JMC1715; 85JOC4861; 83JMC1329).

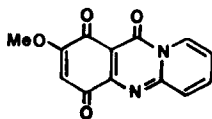
A cyclization approach for derivatives of **290** was elaborated. 2-Acetyl-3-anilino- or -3-methoxy-1,4-benzoquinones have been reported to react with either amidines (76LA1809) or *S*-methylisothiuronium sulfate (71AG442) to give derivatives of **290**, whereas with 2-aminopyridine the tricyclic quinone **291** was obtained (71AG442).

6-Acetamidoquinazoline-2,4,5,8-tetrone and its 6-amino-7-bromo analog were used in amination studies. Both compounds ($pK_a = 5.68$ and 5.62) are completely ionized under basic amination conditions. For example, with aniline in dimethylformamide (DMF) under reflux for 2 min, the 8-imino-phenyl derivative (the 5-iminophenyl derivative is also a possibility) was obtained. A mechanism for this unusual transformation has been postulated (85JOC4861). Quinazoline-5,8-dione undergoes facile cycloaddition with dienes, and in most cases the initially formed cycloadducts undergo oxidative aromatization to give a benzolog of **290** (86JOC2011).

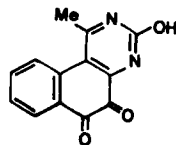
Derivatives of the isomeric quinazoline-5,6-dione were obtained from 6-hydroxyquinazolines after oxidation with oxygen and in the presence of copper(II) acetate and piperidine. These *o*-quinones can be hydrolyzed in



(290)



(291)



(292)

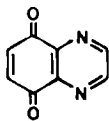
methanolic sodium hydroxide to 6-hydroxy derivatives of **290** (71KGS1698; 72KGS836, 72KGS841; 73KGS1403). In a similar manner, 3-hydroxy-1-methylbenzo[*f*]quinazoline was oxidized with chromium trioxide to the quinone **292** (64JOC2881).

H. PYRAZINE DERIVATIVES

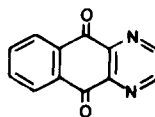
Practically all known quinoxalinediones are derivatives of quinoxaline-5,8-dione (**293**) or its benzologs. The parent quinone and its 2,3-dimethyl analogue were prepared from 5,8-dihydroxyquinoxalines and silver oxide (55MI2; 66ZOR531; 67JOC53). Other derivatives were prepared by either dichromate or FeCl_3 oxidation (64JHC171; 75IJC1009) and the 6,7-dichloro analog was prepared in low yield from the dimethoxy precursor by oxidative chlorination (86JMC1329).

Compounds of the benzo[*g*]quinoxaline-5,10-dione system (**294**) are available either by cycloaddition reactions with **293** or derivatives with dienes (65JOC2583; 86JOC2011) or by condensation of 2,3-diamino-, 2-amino-3-(substituted amino)-, or 2-chloroacetamido-3-chloro-1,4-naphthoquinones under various conditions (55JA35; 67ZOR388; 69FES732; 74JHC377). The benzologs of **294** were prepared from 2-arylamino-3-chloro-1,4-naphthoquinones by treatment with sodium azide and subsequent decomposition of the intermediate azide (63JOC520).

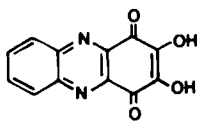
By condensing the sodium salt of rhodizonic acid with *o*-phenylenediamine a quinone was obtained as early as 1888, but the originally proposed structure as a 2,3-dione (1888CB1227) was shown to be incorrect, the compound being in fact **295** (62LA131).



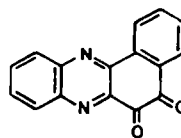
(293)



(294)



(295)



(296)

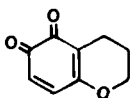
Synthesis of a tetracyclic analog of **294** is also reported from the anhydride of pyrazine-2,3-dicarboxylic acid and a tetralin derivative under Friedel–Crafts conditions (85JCR(S)338). A representative of the *o*-quinonoid system (**296**) was prepared from 2,3-dichloro-1,4-naphthoquinone and *o*-phenylenediamine (63JOC1019).

The polarographic half-wave potentials of substituted quinoxalinediones were measured (67JOC53).

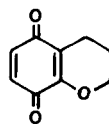
I. PYRAN DERIVATIVES

1. *Chroman- and Isochromandiones*

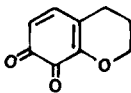
Known are quinones in the chroman (or flavonone, coumarin, or chromone) series [i.e., derivatives of chroman-5,6- (**297**), -5,8- (**298**), and -7,8-dione (**299**) and of isochroman-5,8-dione (**300**)].



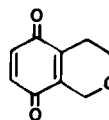
(297)



(298)



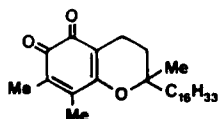
(299)



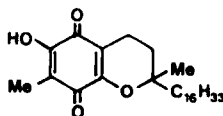
(300)

Few known compounds are 5,6-diones. If α -tocopherol is oxidized with FeCl_3 five products are formed (52SCI34). Two of these were identified as α -tocored (**301**) and α -tocopurple (**302**) (54JA282; 60JA4632). Compound **301** is formed also with other oxidants (39ZPC173). 5,6-Diones are isomerized with hot hydrochloric acid into 5,8-diones (39JA2424; 40HCA455; 41ZPC85; 54JA282).

Coumarin-7,8-diones were prepared from the corresponding dihydroxy precursors after oxidation with PbO_2 or nitric acid (14LA53). A derivative of this system was obtained also from microbiological transformation of a chroman derivative in low yield (71JOC2563).



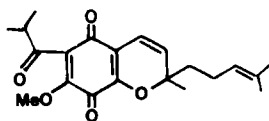
(301)



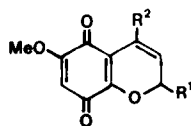
(302)

More compounds are known in the 5,8-dione series. Helinudichromene quinone with the proposed structure **303**, among other compounds, was isolated from *Helichrysum nudifolium* (86P1133). In a few cases oxidative formation of the quinone moiety was the synthetic method for derivatives of **298**. Chromium trioxide was the oxidant (72JCS(P1)2136) and flavone-5,8-diones were prepared in a similar manner, nitric acid being used preferentially (47PIA(A)417, 47PIA(A)427; 48PIA(A)245; 67CB2296; 76JHC361). There are also some special syntheses. Heating 2-hydroxy-3-heptyl-5-anilino-6-isopentenyl-1,4-benzoquinone with aqueous acid causes replacement of the anilino by a hydroxy group and this participated in the formation of a derivative of **298** (53G754; 57MI4). A derivative of **298** was obtained in an attempt to perform the Barbier–Wieland degradation of 4-(2-methoxy-4-methylphenyl)-2,4-dimethylpentan-2-ol (58JCS1007).

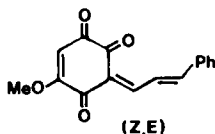
A three-step synthesis of chromen-5,8-diones has been devised from *p*-methoxyphenols in high yield (87S790, 87TL4675). These were in several steps transformed into quinones **304**, which are stable in neutral medium unless $R^1 = \text{Ph}$. In this case the pyran ring spontaneously opens at room temperature to give **305** and **306**. An equilibrium is established between all these forms and the relative proportions are solvent dependent (87S790).



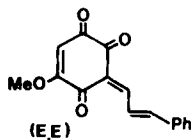
(303)



(304)



(305)



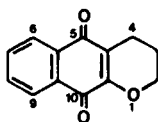
(306)

The biological activity of some chromandiones was studied with regard to their antihemolytic effect on blood (71JPS643). 2,2,7,8-Tetramethylchroman-5,6-dione was shown to be a potent inhibitor of cyclic AMP phosphodiesterase *in vitro* (74BBA173; 75MI1).

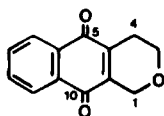
Isochroman-5,8-diones (**300**) were prepared by oxidation of 5,8-dimethoxyisochromans with AgO and nitric acid (82SC279). This system is present as a structural moiety in some natural quinones, such as eleutherin (51HCA561), kalafungin (68MI1), nanaomycins (75MI2, 75MI3; 76CC320), and other compounds.

2. Tricyclic Systems

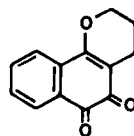
A great number of natural products belong to the naphtho[2,3-*b*]pyran-5,10-dione (**307**) and naphtho[2,3-*c*]pyran-5,10-dione (**308**) ring systems. The angular naphtho[1,2-*b*]pyran-5,6-dione system (**309**) has also been investigated in connection with its formation and isomerization to **307**.



(307)



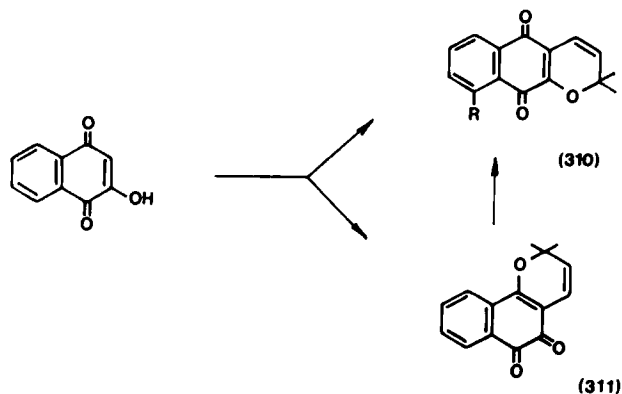
(308)



(309)

a. *Derivatives of Naphtho[2,3-*b*]pyran-5,10-dione and Naphtho[1,2-*b*]pyran-5,6-dione.* Several quinones of these systems were isolated from natural sources; α -lapachone and β -lapachone were most investigated compounds. Both were isolated from a number of South American and other woods.

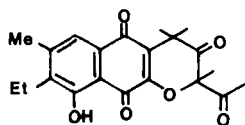
From the earlier investigations of Hooker on the formation of naphthofuran- and naphthopyrandiones from 3-hydroxy-1,4-naphthoquinones having an unsaturated isoprenoid side chain at position 2, up until the present, there are many reports concerning the chemistry of these compounds. Hooker found that 2,2-dimethyl- **307** (α -lapachone) is obtained from the acid treatment of lapachol (1892JCS611, 1896JCS1355; 36JA1190), and similarly oxidation of isolapachol with DDQ gave a mixture of quinones **310** and **311**. The *o*-quinone is isomerized into the *p*-quinone under the influence of acid (67JCS(C)1261, 67JPS86; 69JOC120). Many related compounds cyclize in a similar manner (36JA1190, 36JA1198, 36JA1207; 77CL847). Interconversions of α - and β -lapachone are reversible in sulfuric acid (1892JCS611; 50JA3090), but when lapachol is treated with AlCl₃ only β -lapachone, the



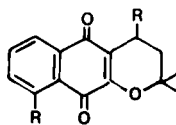
o-quinone, is formed (69IJC457). Extensive investigations of this rearrangement revealed that β -lapachone, being an *o*-quinone, is exceptionally basic, about 800 times more than the *p*-isomer, α -lapachone. In concentrated sulfuric acid, both isomers are converted into their conjugate acids and the cation of the *o*-quinone predominates. In hydrochloric acid, however, where the water content is higher, ionization of β -lapachone is insufficient to shift the equilibrium from the side of the uncharged α -lapachone (50JA3090). Both lapachones are dehydrogenated with DDQ to the corresponding dehydro compounds (67JCS(C)1261). It was also possible to isolate the sulfonated β -lapachone, cyclolapachol sulfonic acid, when lapachol was treated with concentrated sulfuric or chlorosulfonic acid in acetic anhydride (48JA3232). Both lapachones were tested for biological activity. They are active against some gram-positive organisms and show antitumor properties (64MI1; 68MI2, 68MI3; 72MI1). The parent compound (307) shows prothrombin activity (50MI4).

There are some other natural derivatives of 307. From wood extracts of *Catalpa ovata* or *Zeyhera tuberculosa*, in addition to α -lapachone and 310 ($R = H$) the 4-hydroxy and 4-oxo derivatives of 307 were isolated (75CPB384; 76P570; 76TL1795). A 3,4-dihydroxy-2-methyl derivative of 307, cryptosporin, is a metabolite of the fungus *Cryptosporium pinicola* (73HCA619) and annulin B (312), an antimicrobial compound, was isolated from *Garveia annulata* (86JOC5145). In addition to some known quinones like lapachones from the heartwood of *Tabebuia pentaphylla* (*Tecoma pentaphylla*), tecomaquinone II (313) was isolated and synthesized (83IJC(B)866; 85IJC(B)1070).

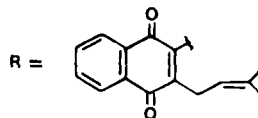
Syntheses of several derivatives of 307 are described, usually in connection with structural elucidation of some natural products (72JCS(P1)380; 75JCS(P1)1936). The parent compound (307) was obtained from 2-chloropropyl-3-hydroxy-1,4-naphthoquinone after treatment with base (50JA5419). Derivatives of this system were also prepared in Michael reactions between



(312)



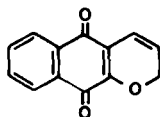
(313)



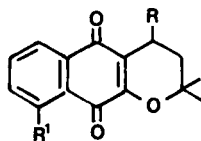
2-hydroxy-1,4-naphthoquinones and benzalacetone (49JA1890) or by the reaction between enamines and the Mannich base 2-dimethylaminomethyl-3-hydroxy-1,4-naphthoquinone (65TL3103; 70JHC1311). The 2-hydroxy analog of **307** was prepared from 2-hydroxy-1,4-naphthoquinone and acrolein (87JMC2005).

There are also natural products of the 3,4-dehydro series (**314**). 3-Methyl-**314** was isolated from heartwood of *Paratecoma peroba* (68N38), and the 2,2-dimethyl derivative (**310**, R = H) from wood of *Rademachera sinica* (81JCS(P1)2764). The last compound (dehydro- α -lapachone) was obtained also from isolapachol and DDQ: **311** is formed first and then isomerized to **310** in the presence of acid (62MI1; 69JOC120; 78CJC517).

Among related compounds, α -caryopterone (**310**, R = OH) was isolated from *Caryopteris clandonensis* (69HCA808), and α -dihydrocaryopterone (**315** = 9-hydroxy- α -lapachone), 9-methoxy- (**316**), and 4,9-dihydroxy- α -



(314)

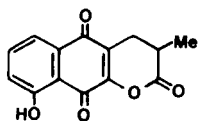


	R	R'
(315)	H	OH
(316)	H	OMe
(317)	OH	OH

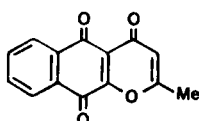
lapachone (**317**) were isolated from wood of *C. ovata* (75CPB384). These compounds were later synthesized (75TL4159; 76JCS(P1)1632; 80TL5083; 85HCA2324).

From *Fomes annosus*, a Basidiomycete fungus, 7-methyl-**310** was isolated and later synthesized, together with the 8-methyl analogue (80P277).

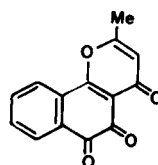
For lambertellin from *Lambertella* fungus, two different structures regarding the position of a hydroxy group were proposed (65JCS5927, 65MI2) and structure **318** was established by synthesis (70JCS(C)109).



(318)



(319)

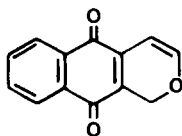


(320)

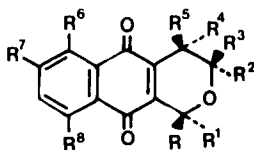
Elbs oxidation of phenolic precursors gave quinones **319** and **320**. These are transformed in the presence of alkali into **319** (66CPB121), which was also obtained in low yield from the aminohydroxy precursor by nitrous oxidation (64CPB307).

b. *Derivatives of Naphtho[2,3-c]pyran-5,10-dione, Tetracyclic, and Higher Systems.* From *Psychotria rubra*, a plant used in Chinese folk medicine, psychorubrin, 3-hydroxy-**308**, was isolated. In the presence of *p*-toluenesulfonic acid it eliminates water to give **321** (87JMC2005). This ring system is found among various naturally occurring compounds (**321**–**329**).

From *Eleutherine bulbosa* two quinones, (+)-eleutherin and (–)-isoeleutherin, were isolated and their structures (**322**, **323**) assigned (50HCA1751; 51HCA561, 51HCA1041). Several syntheses of both compounds have been realized (58HCA213, 58HCA2021; 81CC1277). From *Karwinskia humboldtiana* (Rhamnaceae), 7-methoxy-**322** and 6-hydroxy-**322** were isolated (75JA4985). Several syntheses of these compounds have been realized (58HCA213, 58HCA2021; 81CC534, 81CC1277; 83CC51; 84JCS(P1)2383). In a new synthetic approach, alkanoylquinones were regioselectively alkylated at position



(321)



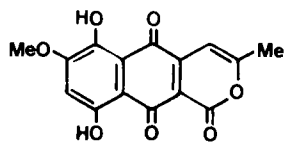
	R	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
(322)	Me	H	H	Me	H	H	H	H	MeO
(323)	Me	H	Me	H	H	H	H	H	MeO
(324)	Me	H	Me	H	H	H	H	OH	OH
(325)	Me	H	Me	H	H	OH	H	OH	OH
(326)	Me	H	Me	H	OH	H	H	OH	OH
(327)	H	H	Me	OH	H	H	OH	OMe	OH
(328)	H	H	Me	OH	H	H	OH	OMe	OMe
(329)	H	H	Me	OMe	H	H	OH	OMe	OMe

3 with alkylsilanes and allylstannanes. Reduction of the side chain carbonyl group, intramolecular oxymercuration, and subsequent reduction with NaBH_4 afforded a mixture of diastereoisomeric naphthopyrans, which were separated and, after oxidation with CAN, yielded eleutherin and isoeleutherin in moderate yield. The same approach was used for the preparation of related compounds (86JOC350). In a related synthesis of **308**, 2-trifluoroacetyl-1-naphthol derivatives were oxidized with CAN to quinones, when simultaneous hydration of the carbonyl group took place. Subsequent alkylation and cyclization led to quinones (86M19).

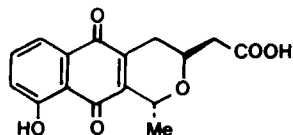
Dimeric naphtho[2,3-*c*]pyrans, containing one quinonoid system, constitute molecules of the aphid pigments deoxyprotoaphin, protoaphin fb, and protoaphin sl (64JCS51; 66JCS(C)1825; 72AJC2199; 83CC51).

From *Fusarium solani* a red pigment, fusarubin (**327**), was isolated. It readily eliminates water and forms a sulfate ester (50LA38; 51LA121). The fungus contains four antibiotic pigments of the fusarubin type (79M14). From *F. oxysporum* seven quinones were isolated. Four of them are heterocyclic, of which three are naphtho[2,3-*c*]pyran derivatives: 9-*O*-methylfusarubin (**328**), 3,6-di-*O*-methylfusarubin (**329**), and 9-*O*-methyl-anhydrofusarubin (3-methyl-7,9-dimethoxy-6-hydroxy-**321**) (85P457). From the fungus *Nectria haematococca*, in addition to the previously known quinones, anhydrofusarubin lactone **330** was isolated (83P1301).

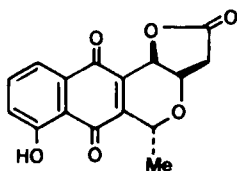
Kalafungin (from *Streptomyces tanashiensis*) (68M11), nanaomycins A, B, C, D, and granaticin (68HCA1257) are members of a family of naturally occurring antibiotics. Nanaomycins were isolated from *Streptomyces rosa* var. *notoensis* (75M12, 75M13; 76CC320). Structures of nanaomycin A (**331**) and D (**332**) (enantiomer of kalafungin) were determined (75M12; 76CC320). Nanaomycin A is converted into nanaomycin D by air oxida-



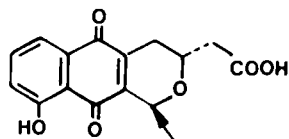
(330)



(331)



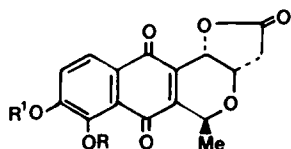
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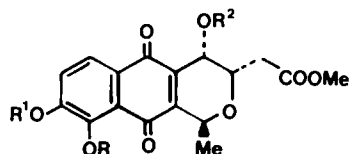
(333)

tion in methanolic solution. Using labeled acetate, it was found that nanaomycin A is biosynthesized from eight acetate units via a polyketide (75MI2). Nanaomycin C is the amide of nanaomycin A, and their biological activities were investigated (75MI3). From *Streptomyces roseofulvus*, deoxyfrenolicin (333) (a degradation product of frenolicin) and frenolicin B were isolated (66JA4109; 78MI4). The absolute stereochemistry of kalafungin was determined as *R,R,R* (76MI5). Several synthetic approaches for nanaomycins, kalafungin, and deoxyfrenolicin have been developed (77T673; 78JA6263, 78JOC4923; 80TL4469; 81JCS(P1)1197; 82CL609, 82JA5850, 82JOC4382; 83CC51, 83JOC2620, 83JOC3439; 84CPB4779, 84JA4181; 85BCJ1699, 85JOC5566, 85MI6, 85T5803, 85T5839; 86CC1568, 86JOC350; 87JOC1174, 87JOC1273).

From *Actinoplanes arizonaensis*, six antibiotics related to kalafungin were isolated: arizonin A1 (344), A2 (335), B1 (336), B2 (337), C1 (338), and C3 (339). The structure of arizonin A1 was confirmed by X-ray analysis (87MI4).



	R	R ¹
(334)	Me	H
(336)	H	Me
(338)	Me	Me

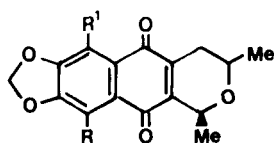


	R	R ¹	R ²
(335)	Me	H	H
(337)	H	Me	H
(339)	Me	Me	Me

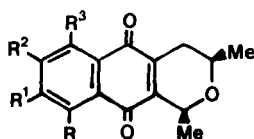
Ventiloquinones are a series of structurally related compounds that were isolated from the rootbark of *Ventilago maderaspatana*. Structures of ventiloquinones A–E (**340**–**344**) are given (85P2373).

Actinorhodin is a dimer and it can exist theoretically in 10 possible tautomeric forms. Studies revealed that in solution the predominant tautomer is **345** (68CB4221). An enantiomer (C-1, C-3 = *S*, *R*) was synthesized by degradation of a naphthocyclinone with diazomethane (83LA510; 87LA297). Actinorhodin is biosynthesized from acetate units by the polyketide pathway (81JOC455).

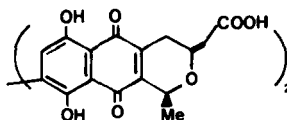
The structure of the antibiotic lactoquinomycin has been proposed on the basis of spectroscopic data. It is related to kalafungin, having a sugar moiety (**346**) (85MI7).



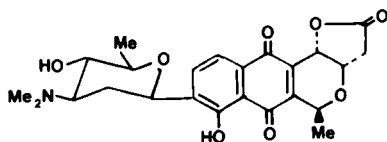
	R	R ¹
(340)	MeO(OH)	OH(OMe)
(341)	MeO	MeO



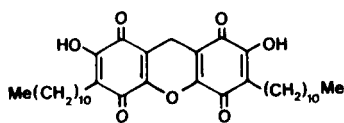
	R	R ¹	R ²	R ³
(342)	OH	OMe	OMe	OH
(343)	OH	OH(OMe)	OMe(OH)	OH
(344)	OMe	H	OMe	OMe



(345) C₁, C₃ = *R*, *S*



(346)



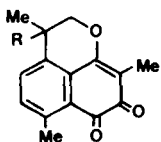
(347)

A diquinonoid system is incorporated in anhydrovilangin (**347**), which is obtained from vilangin, isolated from berries of *Embelia ribes* and after treatment with hot sulfuric or orthophosphoric acid (61JOC4529). Analogs of vilangin can be prepared from hydroxy-1,4-naphthoquinones with various aldehydes (62T361; 64T2967; 67T817), a reaction which was reported as early as 1888 (1888CB2203).

Mansonones are a group of 10 related quinones isolated from *Mansonia altissima*, *Thespesia populnea*, or *Ulmus* spp. (66TL2767; 71MI1). Mansonone I (**348**) and mansonone F (**349**) have been synthesized (86AJC647) and **348** can be dehydrated to **349**, which can, in turn, be hydrogenated to mansonone E (**350**).

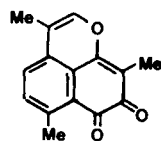
Structurally related is biflorin (**351**), isolated from *Capraria biflora*, and the first naphtho[1,8-*bc*]pyranquinone found in nature. It has antibiotic properties. Its structure was determined by Prelog and co-workers (58HCA1386; 63HCA409, 63HCA415) and it was synthesized by an intramolecular Diels-Alder addition between a benzyne and furan (86AJC647).

From a *Streptomyces* strain an antibiotic sarubicin (**352**) was isolated and its structure was established by X-ray analysis (80MI1; 80MI3).

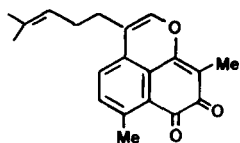


(348) R = OH

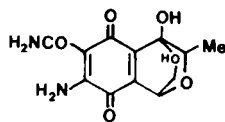
(350) R = H



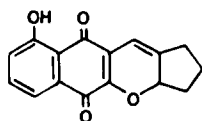
(349)



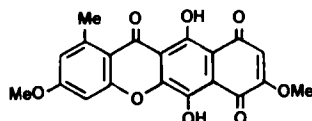
(351)



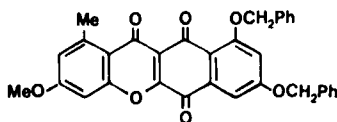
(352)



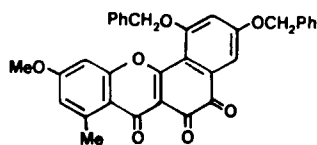
(353)



(354)



(355)

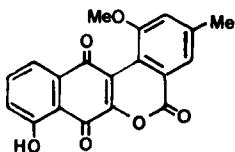


(356)

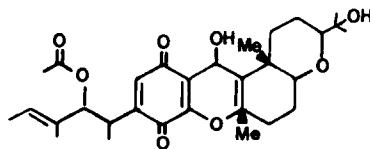
From the slime mold *Metatrichia vesparium* (Myximycetes), a red pigment, vesparion (353), was isolated and its structure was established from spectroscopic data and by synthesis (87LA793).

Bikaverin, a red pigment with antiprotozoal activity isolated from *F. oxysporum*, *Giberella fujikuroi*, and *Mycogone iadpai*, has the structure 354 (71JCS(C)2786, 71JCS(C)2788, 71JCS(C)2792). After the total synthesis (76JCS(P1)499), in an another approach cyclization of an aroyl-naphthalene gave two isomeric products, and after dichromate oxidation the two isomeric quinones 355 and 356 were obtained (77CC645).

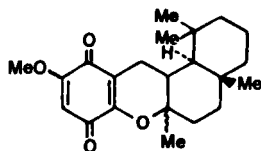
A pigment WS 5995 (357) was isolated from *Streptomyces aurantiacolor* and synthesized (80MI4, 80TL4359). The parent unsubstituted system was prepared from 2-hydroxy-1,4-naphthoquinone and diazotized anthranilic acid (38CB2703). Stemphone (358) is a yellow metabolite from *Stemphylium sarcinaeforme* (75AX(B)108). From the sponge *Stelospongia conulata*, three heterocyclic quinones were isolated: cyclosporgiaquinone-1 (359), its dehydro derivative, and cyclosporgiaquinone-2 (360), for which an X-ray study confirmed its structure (78AJC2685).



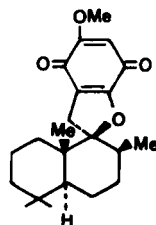
(357)



(358)

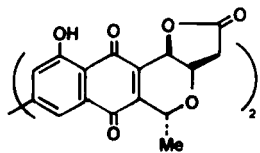


(359)

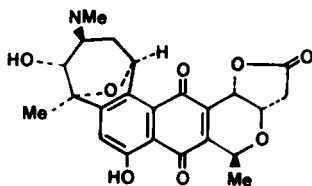


(360)

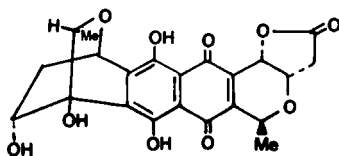
A dimeric quinone, the antibiotic crismycin A (**361**), was isolated from *Micromonospora purpureochromogenes* (86MI6). Antibiotic **362** was isolated from a *Thermomonospora* species, and its structure, which resembles granaticin, was determined by X-ray analysis (87TL4485). The antibiotic granaticin (**363**) is produced by *Streptomyces olivaceus* and other actinomycetes. Its structure was confirmed by X-ray analysis, and the compound may be regarded as a structural hybrid of sarubicin A and nanaomycin D (68HCA1257, 68HCA1269). Two synthetic approaches toward the synthesis of **363** were developed and it was synthesized in 20 steps in 2% overall yield (87H167, 87JA3402). In addition to **363**, there were isolated from *Streptomyces thermoviolaceus* dehydrogranaticin (**364**) and two structurally related quinones. Some model compounds containing these chromophores were synthesized (77T673). Biosynthetically granaticin is formed from eight acetate



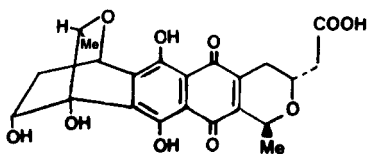
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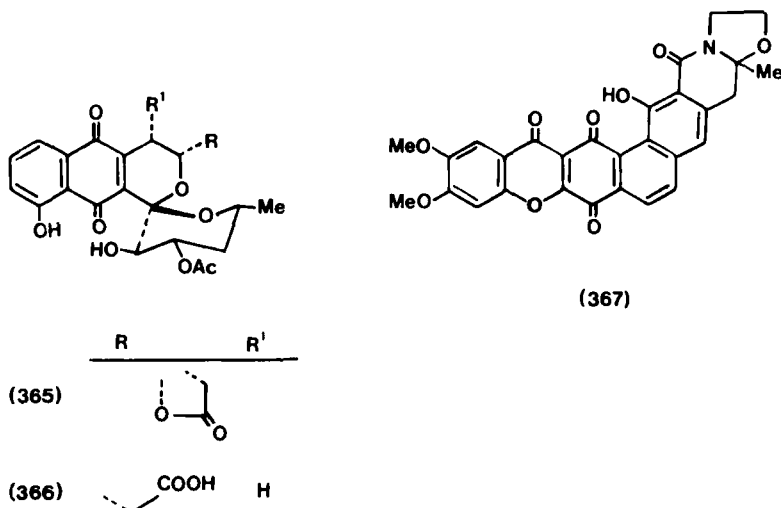
(362)



(363)



(364)



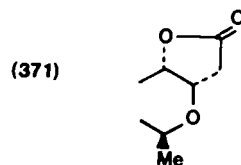
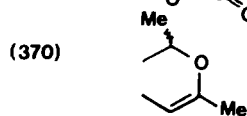
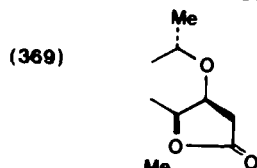
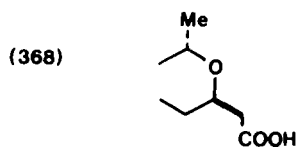
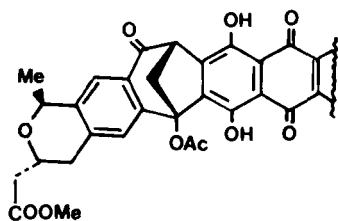
units and one glucose, the latter being converted into 2,6-dideoxyhexose (79JA701).

Antibiotics griseusin A (365) and B (366) were isolated from *Streptomyces griseus* (76MI1, 76T2207) and later using the X-ray structure determination of a derivative, the revised absolute configuration was established (83TL389).

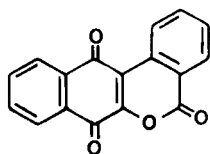
A heptacyclic antibiotic cervinomycin is composed of compound A₁ and the quinone cervinomycin A₂ (367), the structure of which was determined by NMR spectroscopy (86JA6088).

From mycelium of a *Streptomyces* strain, yellow, red, and violet pigments, naphthocyclinones, were isolated (74LA1063, 74LA1100; 83LA471). Their structural assignments are based mainly on chemical transformations and NMR spectroscopy. Stereochemical features of the γ -naphthocyclinone (369) follow from its crystal structure determination (83LA503). Structures of β - (368), ϵ - (370), and γ -isonaphthocyclinone (371) are given. Tautomeric equilibria were studied together with actinorhodins by means of ^{13}C NMR and circular dichroism. It was found that the naphthazarin chromophore tautomerizes so rapidly that ^{13}C -NMR spectra exhibit only one average signal for each carbon atom (87LA751). The biosynthetic pathway has been established and acetate and malonate units are involved in the polyketide pathway (78JOC1438).

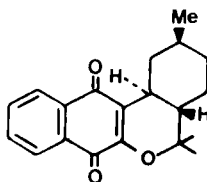
There are only a few synthetic approaches toward these polycyclic systems. The coupling product from diazotized anthranilic acid and 2-hydroxy-1,4-naphthoquinone is transformed into 372 by heating with acetic anhydride (83IJC(B)95). The same quinone reacts with citral and, depending on the reaction conditions, several products are formed. In a triethylamine-catalyzed reaction, the angular quinones 373 and 374 are formed, whereas acid-catalyzed condensation gives the linear compound 375 (82SC195;



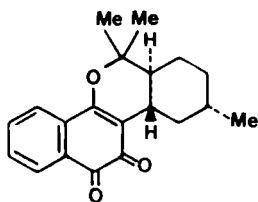
86JCS(P1)659). For condensation products with other aldehydes, a linear pentacyclic structure was proposed, but not proved (1894JCS76). 2-Chloro- or 2,5-dichloro-1,4-benzoquinones are arylated with diazotized anthranilic acid; the reaction is postulated to proceed via a pentacyclic quinone **376**, which was isolated in low yield (59JCS3250).



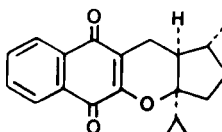
(372)



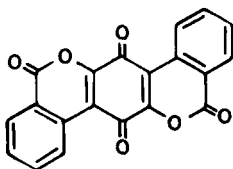
(373)



(374)



(375)



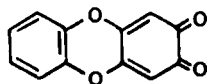
(376)

J. DERIVATIVES OF 1,4-DIOXANE, 1,4-DITHIANE, AND 1,4-OXATHIANE

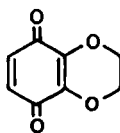
1. 1,4-Dioxane Derivatives

Catechol is oxidized with polyphenol oxidase to the yellow quinone **377** (57BBA155; 60BBA322), and the related 6,7-dioxobenzo-1,4-dioxane was prepared by oxidation of the monohydroxy precursor with Fremy's salt or from the dimethoxy precursor with nitric acid (63ZOB2066). The isomeric system **378**, its benzoanalog, and derivatives thereof were obtained similarly by oxidation of either the parent system or hydroxy and/or amino analogs (54RTC513; 55RTC31; 79ZN(B)624).

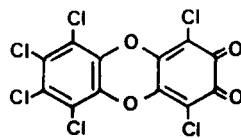
Condensation of tetrachloro-1,2-benzoquinone or 2,3-dichloro-1,4-naphthoquinone with *o*-dihydroxyarenes, alone or in the presence of copper and its salts, yields **379** or **380** (01JA10; 07JA7; 08JA499; 21CB259; 52JCS489; 78IZV204).



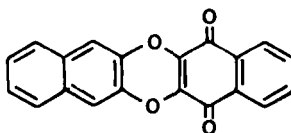
(377)



(378)



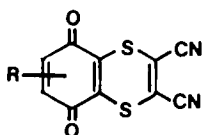
(379)



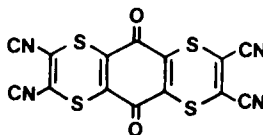
(380)

2. 1,4-Dithiane Derivatives

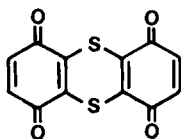
In general, these compounds were prepared from 2,3-dichloro- or tetrachloro-1,4-benzoquinones and disodiumdimercaptomaleonitrile to give **381** or **382** (69AP285), or from 2,3-dichloro-1,4-naphthoquinone and sodium sulfide or ammonium dicarbamate to give **383** or derivatives thereof (21CB594; 22CB2543; 51JA3459; 69CB1739). A typical transformation of these systems is the extrusion of one sulfur atom upon heating, or after treatment with hydrogen peroxide or peracetic acid (22CB2543; 69AP53, 69AP285, 69CB1739, 69CB2378), to give thiophene derivatives **162**, **157**, **384**, or benzo analogs.



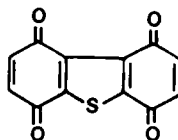
(381)



(382)



(383)

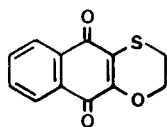


(384)

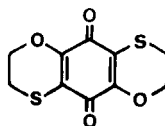
Benzo analogs of **381** were obtained in a Friedel–Crafts reaction from 2,3-dicyano 1,4-dithiin-5,6-dicarboxylic acid anhydride and benzene (62M12), or from 2,3-dichloro-1,4-naphthoquinone and 1,2-dimercaptoethane (67RC1067). Reduction potentials of several quinones were determined (86CC1489).

3. 1,4-Oxathiane Derivatives

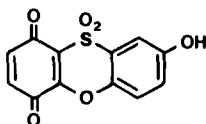
Compounds **385** and **386** were prepared from quinones with a chlorine atom and an aziridino group in ortho positions after treatment with sodium hydroxyethylmercaptide (57AG252). Oxathiin *S,S*-dioxide quinone (**387**) was obtained from the bis(2,5-dihydroxyphenyl)sulfone in the presence of sodium chlorate and sulfuric acid (73CB798).



(385)



(386)

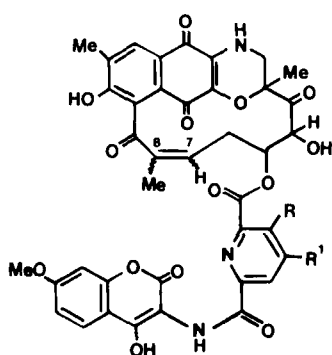


(387)

K. DERIVATIVES OF 1,4-OXAZINE AND 1,4-THIAZINE

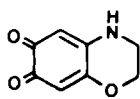
1. 1,4-Oxazine Derivatives

Rubradirins are secondary metabolites of various strains of *Streptomyces achromogenes* (64AAC91; 78MI3). The structures of rubradirin (388), rubradirin B (389), and rubradirin C (390) have been elaborated (82JA5173). Molecules are built up from a quinone part with an ansamycin-like moiety, and esterified with pyridine-2,6-dicarboxylic acid derivative, which is linked to a coumarin moiety. Rubradirin is a glycoside with a nitro sugar, rubranitrose. After hydrolysis, the pyridine and coumarin parts are split off to give rubransarols (64AAC91; 65AAC97; 78MI5; 79MI5). For rubransarol B, an X-ray structure determination was made; its absolute configuration is 2*S*, 4*S*, 5*R*, 6*S* (78MI5; 82JA5173). With regard to antibiotic activity, rubradirin is the most important member of this group.

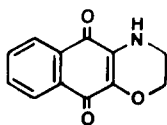


	C ₇ -C ₈	R	R ¹
(388)	cis	OH	
(389)	trans	OH	H
(390)	trans	H	H

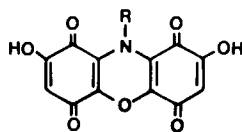
Synthetically, 2,3-dihydro-1,4-benzoxazine-6,7-diones (**391**) can be prepared from 2,5-bisanilino-3-acetyl- (or methoxycarbonyl)-1,4-benzoquinones and substituted 2-hydroxyethylamines (73T2881). 2-Amino-3-aziridino-1,4-naphthoquinone, when heated in aqueous sodium hydroxide, is claimed to give **392** (69FES732), and the benzo analog was prepared from 2,3-dichloro-1,4-naphthoquinone and tosylated *o*-aminophenol (21CB259). Compound **392** was prepared from 1,4-naphthoquinone and β -alanine (66MI2). When 2,5-dihydroxy-1,4-benzoquinone was condensed with various nitroso compounds, derivatives of **393** were obtained (65T389).



(391)



(392)



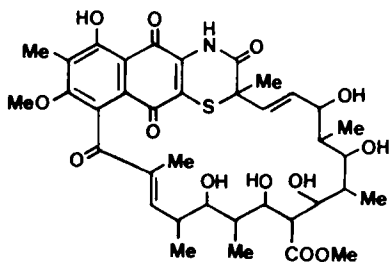
(393)

2. 1,4-Thiazine Derivatives

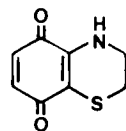
An antibiotic, ansathiazin (**394**), was isolated from *Streptomyces albolongus*; the structure followed from its transformations and spectroscopic data (86E1167).

Synthetically, 7-methyl- **395** was obtained from 4-methyl-1,2-benzoquinone and 2-aminoethanethiol (70JHC555) and 3-oxo analogs of **395** were prepared from azidobenzoquinones and ethyl mercaptoacetate (73TL4695). Dibenzo and benzo or naphtho analogs of **395** were prepared from 2-arylmino-3-mercapto-1,4-naphthoquinones on air oxidation (22LA281; 24CB496).

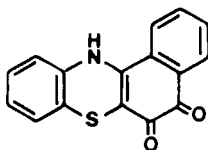
From 3-chloro-1,4- or -1,2-naphthoquinones and sodium sulfide, the benzolog of **395**, and with *o*-aminothiophenol the isomeric quinone **396**, were prepared (71ZOR1031; 86JCS(P1)2233). Compound **396** rapidly isomerizes



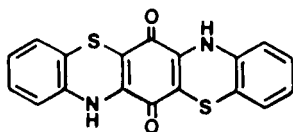
(394)



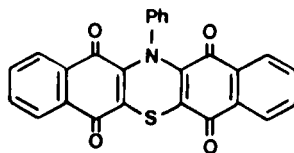
(395)



(396)



(397)



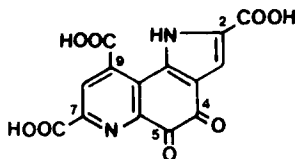
(398)

into the enol when dissolved in methanol; this form is also obtained when **396** is crystallized from hot solvent (86JCS(P1)2233). The pentacyclic quinone **397** was obtained by oxidative cyclization of the dimercapto precursor in the presence of air (28CB1395) or upon treatment of 3,6-dianilino-2,5-dichloro-1,4-benzoquinone with sodium sulfide and subsequent oxidation with oxygen (27MI1). 2,3-Dichloro- and 2-anilino-3-chloro-1,4-naphthoquinone reacted with sodium sulfide to produce the pentacyclic quinone **398**. The compound, when heated in nitrobenzene or in acetic/nitric acid, extrudes sulfur and compound **61** ($R = Ph$) is formed (23CB1291).

VII. Quinones with Two Different Heterocyclic Systems Attached to the Quinone Moiety

A. PYRROLOQUINOLINEQUINONES

A novel class of dehydrogenases, quinoproteins, has been discovered. The coenzyme methoxatin or pyrroloquinolinequinone (**399**, PQQ) is widely distributed in many organisms (81MI4; 84MI1). The dehydrogenases are neither flavin nor nicotinamide dependent. PQQ is a prosthetic group of various important oxidoreductases from procaryotes as well as eucaryotes, such as alcohol dehydrogenase, aldehyde dehydrogenase, D-glucose dehydrogenase,



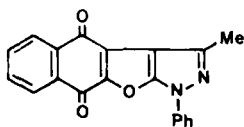
(399)

copper-containing amine oxidase, amine dehydrogenase, choline dehydrogenase, nitroalkane oxidase, polyethylene glycol dehydrogenase, and polyvinyl alcohol dehydrogenase (79MI6; 80BBA370; 81ABC851, 81MI5; 83TL3465; 84ABC561, 84ABC3099, 84MI2, 84MI3; 85ABC1001, 85ABC1071, 85ABC1227, 85ABC3623, 85JA3328, 85MI8; 86ABC49, 86BBR1279; 87MI5). PQQ shows a specific stimulating effect on microbial growth (84ABC2873, 84ABC2909; 85ABC699). Quinoprotein alcohol dehydrogenase from *Pseudomonas aeruginosa* has been shown to contain two moles of PQQ per mole of enzyme (84BJ921). PQQ oxidizes amines and amino acids under aerobic conditions and, for example, phenylalanine is transformed into a mixture of phenylacetaldehyde and phenylacetic acid (84TL4753). Thiols are also oxidized in the presence of PQQ into disulfides (85CL135). PQQ can be reduced by various reagents, such as thiophenol, $\text{Na}_2\text{S}_2\text{O}_4$, NaBH_4 , and 1-benzyl-1,4-dihydronicotinamide (86BCJ1911).

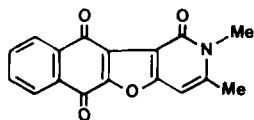
The structure of PQQ was determined by X-ray analysis (79N(L)843). Thereafter, several syntheses of PQQ were described (81JA5599, 81JOC4317; 82JOC1148, 82JOC2833; 83CC1372; 85JA5555, 85MI9; 86T3259). In addition, a total synthesis of 9-decarboxy-399 (87JOC1942) and 7,9-bis-(decarboxy)-399 (85JA3328) were described. The latter forms a C-5 adduct with acetone and a cyclic adduct with urea. The quinone moiety is hydrated and, under vigorous conditions, ring contraction in this part of the molecule takes place. The quinone is still capable of oxidizing primary, but not secondary, amines (85JA3328).

B. OTHER SYSTEMS

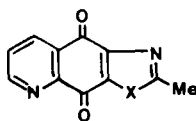
2,3-Dichloro-1,4-naphthoquinone and 3-methyl-1-phenylpyrazolone gave **400**, and the tetracyclic quinone **401** was obtained from 1,2-dimethyl-4-hydroxy-6-pyridone (47CB47). Cyclization of 6-acetylamino-7-chloroquinoline-5,8-dione in the presence of acetic anhydride yielded the oxazolo derivative **402**, and from the 7-mercapto analog the thiazole quinone **403** was



(400)

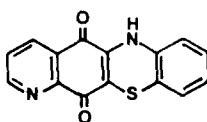


(401)

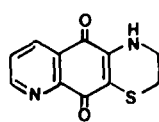


(402) X = O

(403) X = S



(404)



(405)

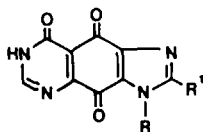
formed. The related 6-anilino-7-mercapto precursor was transformed into **404**, and **405** was prepared from the 6-chloroethylamino analog (59LA108).

Imidazo[4,5-*g*]quinazoline-4,9-diones (**406**) were synthesized as purine mimics. They were obtained from the 4-amino precursor and Fremy's salt or from the 4,9-unsubstituted derivatives with nitrogen dioxide. In strong acid, a diprotonated quinone is present (86JOC4784).

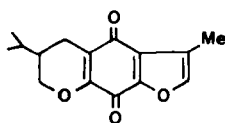
From Cyperaceae, many quinones with the **407** skeleton (scabequinones) were isolated, among others (73TL3; 78P263). Total synthesis of racemic scabequinone (**407**), a major component of *Cyperus scaber*, from a benzofuran derivative has been described (73CC718).

The corresponding lactone, **408**, was obtained either by dichromate oxidation of Byak-angelicin, a component of the root of *Angelica glabra* Makino (38CB344), or by nitric acid oxidation of 6,7-dihydroisopimpinellin (74JHC1119). Lactone **408** is also obtained from 9-methoxypsoralene (xanthotoxin) and chromium trioxide or from 4-amino-9-methoxypsoralene (12CB3705; 59JOC523).

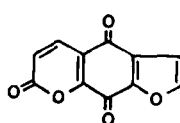
Khellinequinone (**409**) was obtained either by oxidation of the mono-hydroxy or dihydroxy precursor with Fremy's salt (60CB2829) or vanadium



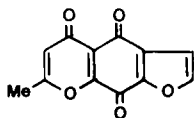
(406)



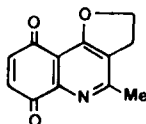
(407)



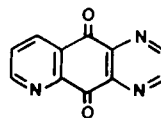
(408)



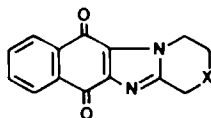
(409)



(410)



(411)

(412) $X = \text{CH}_2, \text{O}$

pentoxide (87MI6), or by nitric acid oxidation of the dimethoxy precursor (49PIA(A)107).

Compound **410** was prepared from 4-chloro-3-chloromethyl-5,8-dimethoxy-2-methylquinoline. In hot acetic acid the furan ring was formed and dichromate oxidation gave the product (65MI1).

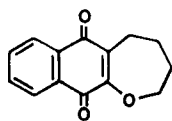
Addition of 1-(dimethylamino)-3-methyl-1-azabuta-1,3-diene to quinoxaline-5,8-dione gave a derivative of **411**. The initial cycloadduct eliminated dimethylamine and subsequent oxidation was effected with air or Ag_2O (87JOC2285).

3-Chloro-2-piperidino- or -2-morpholino-1,4-naphthoquinones were treated with sodium azide and the intermediate azido compounds decomposed thermally to give quinones **412** (63JOC524).

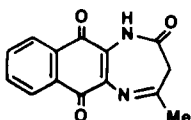
VIII. Miscellaneous Heterocyclic Quinones

Few quinones with a condensed seven-membered heterocyclic ring are known. Compound **413** was prepared from 3-(4'-chlorobutyl)-2-hydroxy-1,4-naphthoquinone, sodium iodide, and carbonate (67JPS86). 2,3-Diamino-1,4-naphthoquinone reacted with diketene to give a product to which structure **414** was assigned. The product is easily hydrolyzed to the starting diamino compound (67ZOR162). Quinones with an eight-membered ring (**415**) were obtained as intermediates in the total synthesis of porfiromycin (77JA8115).

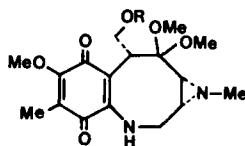
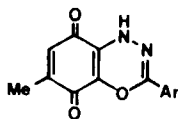
4,1,2-Benzoxadiazine-5,8-diones (**416**) were prepared from 2-bromo-6-methyl-1,4-benzoquinone and aromatic acylhydrazides (85IJC(B)307). Quinones with a triazolo-1,3,4-thiadiazine ring (**417**) were prepared from 2-bromo-3-hydroxy-1,4-naphthoquinone and 4-amino-3-aryl-5-mercapto-1,2,4-triazoles (86OPP104).



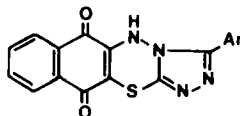
(413)



(414)

(415) R = H, Ph, C₆H₅

(416)



(417)

IX. Appendix

After preparing the manuscript some important contributions to the chemistry of heterocyclic quinones appeared in the literature. A review article about pyranonaphthoquinone antibiotics was published (86YGK918).

A general regiospecific synthesis of annulated heterocyclic quinones is described. It involves thermal rearrangement of 4-heteroaryl-4-hydroxycyclobutenones to the corresponding annulated hydroquinones. Examples with heteroaryl groups, such as *N*-methylpyrrolyl, furyl, and thienyl, are described. The corresponding quinones were obtained after oxidation with Ce(IV)/SiO₂ reagent (88JOC996).

A total synthesis of (±)-mitomycins via isomitomycin A is described (87JA7881), and from a mitomycin rearrangement albomitomycin A and isomitomycin A were formed from mitomycin A (87JA7224). Amidine derivatives were prepared from mitomycin C and formamide acetals. These, when treated with amines, afforded the corresponding 7-*N*-substituted mitosanes (87JOC5601).

A synthesis of the carbazolequinone alkaloid murrayaquinone-B, previously isolated from the root bark of *Murraya euchrestifolia*, is described and the compound was obtained in 13% yield (88JCS(P1)241). Photolysis of 2-amino-1,4-naphthoquinone afforded the pentacyclic quinone **61** (R = H) and some of its *N*-substituted derivatives (88TL591). From 2,3-dibromo-5,6-dimethyl-1,4-benzoquinone, ethyl acetoacetate, and pyridine, a derivative of the indolequinone system related to **65** was prepared (87IJC180).

In the furoquinone series, a new compound, isotanshinone, was isolated. The compound has a benzo analog skeleton of **84** (87MI7). The preparation of 3-methylbenzofuran-4,5-dione is described and its dienophilicity was studied (87TL3427). A direct synthesis of some heterocyclic quinones is reported. The method is a direct one-step ortho-bisacylation of hydroquinones under very mild conditions and in the presence of AlCl_3 . Examples of acylation with furan-3,4- and pyridine-3,4-dicarboxylic acid dichlorides are described (87TL1533).

Several benzimidazole-4,7-diones were synthesized and tested for anti-tumor activity (88JMC260). There is also a report on oxidation of 4-amino- or 4-alkoxybenzo-2,1,3-thiadiazoles with hydrogen peroxide in concentrated hydrochloric acid to give 5-chlorobenzo-2,1,3-thiadiazole-4,7-dione (88KGS114).

Several substituted quinoline-5,8-diones were prepared in connection with the synthesis of partial structures of lavendamycin and streptonigrin (87JHC1253, 87JMC1918). Similar syntheses were described in connection with the preparation of phomazarin (**247**) (87JHC1649). A total synthesis of the antibiotic bostrycoidin (**283**) is described. The synthesis is based on selective lithiation of *N,N*-diisopropylnicotinamide followed by condensation with *N,N*-dimethyl-2,3,5-trimethoxybenzamide (87T5281). In the saframycin series the structure of saframycin D, an antitumor antibiotic, has been determined by various NMR techniques. The compound is also a dimeric isoquinoline-quinone derivative (87CPB440). Moreover, a total synthesis of the isomeric saframycin B and some of its congeners is described (87CPB2158).

Selective reduction of xiloidone (**310**, $\text{R} = \text{H}$) is reported. Catalytic reduction in acetic acid gave the compound with the reduced aromatic ring and the double bond in the pyran ring whereas in tetrahydrofuran only the latter was reduced (87JCR(S)26). Crown ethers with a 1,4-benzoquinone ring as part of the molecule were synthesized from pyrogallol. Further treatment with butadiene and subsequent oxidation afforded the naphtho analogs. Their redox potentials were determined and charge-transfer complex formation with some biogenic amines was observed (88JCS(P1)511).

Derivatives of pyrroloquinolinequinone (PQQ, **399**) were prepared as model compounds of a novel coenzyme (87S1067). 2,3-Disubstituted quinoxaline-5,8-diones were prepared by oxidation of the corresponding hydroquinones with Ag_2O . They underwent dipolar cycloaddition to give derivatives of pyrazolo[3,4-*g*]- and isoxazolo[4,5-*g*]quinoxalinequinone (87H3173).

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The Chemistry of Thiophenium Salts and Thiophenium Ylids

ALEXANDER E. A. PORTER

*Chemistry Department, University of Stirling,
Stirling FK9 4LA, Scotland*

I. Introduction	152
II. S-Alkylated Thiophenes	153
A. S-Alkylation of Thiophene and Its Derivatives	153
B. Spectroscopic Properties of S-Alkylated Thiophenes	155
1. Ultraviolet Spectroscopy	155
2. Nuclear Magnetic Resonance Spectroscopy	156
3. Mass Spectroscopy	156
C. Structure of S-Alkylthiophenium Salts	158
D. Reactions of S-Alkylthiophenium Salts	159
III. Thiophene S,C-Ylids	159
A. Introduction	159
B. Structure and Bonding in Thiophene S,C-Ylids	162
C. Reactions of Thiophene S,C-Ylids	165
1. Introduction	165
2. 2-Substituted Thiophene Formation	167
3. 2 <i>H</i> -Thiopyran Formation	167
4. 2-Thiabicyclo[3.1.0]hex-3-ene Formation	168
5. 3-Substituted Thiophene Formation	168
6. Oxathiocin Formation	169
7. Carbenic Fragmentation	170
8. Cycloaddition Reactions	171
D. Mechanism and Energetics of the Formation of the Different Product Types	171
IV. Thiophene S,N-Ylids	176
A. Introduction	176
B. Synthesis of Thiophene S,N-Ylids	176
C. Structure of Thiophene S,N-Ylids	176
D. Reactions of Thiophene S,N-Ylids	177
1. Sulfur-Nitrogen Bond Cleavage	177
2. Cycloaddition Reactions	177
3. Oxidation of Thiophene S,N-Ylids	178
E. General Considerations on the Reactions of Nitrenes with Thiophene	179
V. Conclusions	182
References	182

I. Introduction

The π -excessive heterocycles are generally regarded as aromatic in their reactions, by the criterion of electrophilic substitution (67MI1), although it is now recognized that such a classification is a gross oversimplification (79MI1). The aromaticity of the π -excessive heterocycles is in little doubt, as evidenced by the deshielding effects of the ring current on the ring protons, and is explained in terms of a planar sp^2 -hybridized carbon framework bonded to an sp^2 -hybridized group V or group VI heteroatom.

In the case of the group V π -excessive heterocycles, the single lone pair of electrons is associated with a p_z orbital orthogonal to the plane of the ring and overlap occurs with the p_z orbitals of the carbon framework to give a complement of six π electrons, the "aromatic sextet." This involvement of the pair of electrons from the heteroatom with the closed aromatic shell effectively renders the group V π -excessive heterocycles nonbasic.

With the group VI π -excessive heterocycles, the situation is different in that sp^2 hybridization of the heteroatom results in two lone pairs of electrons: one in a p_z orbital in a plane orthogonal to the ring that is donated to form the complement of six π electrons necessary for aromaticity, and the second in an sp^2 hybrid orbital in the plane of the ring. In principle, this lone pair of electrons could participate in reactions without affecting the aromaticity of the ring, provided that such a reaction had no effect on the hybridization of the heteroatom.

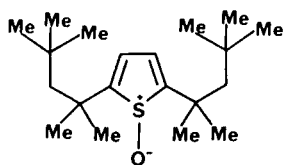
In the case of furan, the nucleophilicity of the lone pair of electrons on oxygen is not expected to be significant in view of the electronegativity of the oxygen atom. However, thiophene, selenophene, and tellurophene are expected to be significantly more reactive because of the decrease in electronegativity and increase in size of the heteroatom on descending the group. In addition, sulfur, selenium, and tellurium have available d orbitals that could participate in $d\pi-p\pi$ bonding.

In the case of furan, there are no known reactions involving the oxygen atom. In contrast, the ability of the sulfur atom of thiophene to form unstable sulfoxides and sulfones is well known (85HC(b)). Moreover, when certain stabilizing substituents are present, both sulfoxides and sulfones may be isolated and characterized, thus providing adequate evidence of the reactivity of the sulfur atom.

The geometry at sulfur in the case of the sulfoxides is of fundamental importance, because if the oxygen atom lies in the plane of the ring, then aromaticity could still be preserved. If however, the sulfoxide adopts the normal tetrahedral arrangement of the sulfur atom, then severe disruption of the aromatic character of the ring is to be expected due to a twisting of

the lone pair, thus limiting effective overlap with the p_z orbitals of the carbon framework.

Spectroscopic evidence suggests that the sulfur atom in 2,5-di-*t*-butylthiophene 1-oxide is tetrahedrally hybridized, with the S—O stretch occurring at $9.5\ \mu\text{m}$. Perhaps the most striking evidence confirming the tetrahedral character of the sulfur atom is the dynamic ^1H -NMR spectra of 2,5-bis(1,1,3,3-tetramethylbutyl)thiophene 1-oxide (**1**) (70JA7610). At 263 K, the geminal methylene protons in the side chain are diastereotopic and resonate as an AB quartet, necessitating a pyramidal sulfur atom. As the temperature increases, inversion at sulfur becomes more facile until, at 333 K, the protons become equivalent. From these data, the free energy of activation for inversion at sulfur was shown to be $14.8\ \text{kcal mol}^{-1}$. This figure falls within the range predicted by molecular orbital calculations.



(1)

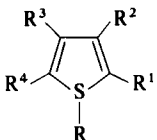
In the case of the sulfones, all of the valence shell electrons of the sulfur atom are utilized in bond formation and, as such, none remains to contribute to the π system of the ring. Thus, the sulfones would be expected to behave as reactive conjugated dienes. Indeed, it is to be expected that thiophene 1,1-dioxides should be more reactive than the corresponding thiophene 1-oxides, a prediction that is not borne out in practice since, for example, in Diels–Alder reactions the sulfoxides tend to be somewhat more reactive than the sulfones (76ACS(B)353).

II. S-Alkylated Thiophenes

A. S-ALKYLATION OF THIOPHENE AND ITS DERIVATIVES

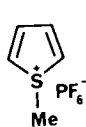
The first report on the alkylation of thiophene at sulfur appeared in 1964 when Brumlick and co-workers reported that thiophene could be methylated at sulfur using trimethyloxonium tetrafluoroborate or methyl iodide/silver perchlorate (64JA5360). In this work, the position of methylation was con-

TABLE I
 S-ALKYL THIOPHENIUM SALTS

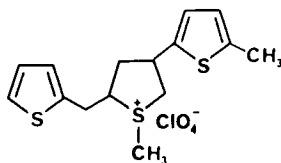
						
X	R	R ¹	R ²	R ³	R ⁴	Yield (%)
PF ₆ ⁻	Me	H	H	H	H	10
ClO ₄ ⁻	Me	H	H	H	H	5
PF ₆ ⁻	Me	Me	H	H	Me	12
ClO ₄ ⁻	Me	Me	H	H	Me	5
PF ₆ ⁻	Et	Me	H	H	Me	3
PF ₆ ⁻	Me	—CH ₂ CH ₂ Ph	H	H	H	33
PF ₆ ⁻	Me	Me	CH ₂ D	CH ₂ D	Me	95
PF ₆ ⁻	Me	Me	H	Me	H	12
ClO ₄ ⁻	Me	Me	H	Me	H	5
PF ₆ ⁻	Me	Me	Me	Me	Me	95
PF ₆ ⁻	Et	Me	Me	Me	Me	95
PF ₆ ⁻	Me	H	Me	H	H	10
PF ₆ ⁻	Et	Me	H	Me	H	3
(PF ₆ ⁻) ₂	Me	2-(1'-methyl-2-pyridinio)ethyl	H	H	H	35

firmed by cation exchange studies using the stable hexafluorophosphate salt 2. Compound 2 was characterized by elemental analysis and by hydrogenation to form 1-methyltetrahydrothiophenium hexafluorophosphate, which was also synthesized independently from thiophane.

Unfortunately this work was never described with full experimental conditions and several groups have experienced considerable difficulty in reproducing the results. In my laboratory, trimethyl- or triethyloxonium tetrafluoroborate failed to give any observable product. Subsequently it was demonstrated that low yields of the S-alkylated thiophenes could be obtained using the methyl iodide/silver perchlorate procedure, but the reaction conditions were critical and on at least one occasion when the ratio of thiophene to the alkylating agent was reduced a spontaneous detonation occurred (70JCS(C)1764). This obvious problem may be circumvented by using silver tetrafluoroborate in place of the perchlorate. Even under the most carefully controlled conditions, the yields of the S-alkylated thiophenes are usually low and in some instances (Table I) it has only proved possible to characterize the products spectroscopically. All available data suggest that, although in favorable cases it is possible to alkylate thiophene and certain derivatives at



(2)



(3)

sulfur, certain limitations are observed. Mesomerically deactivated thiophene derivatives, such as acyl-, cyano-, or nitrothiophenes, fail to react. In addition, side reactions may occur with inductively activated derivatives. Thus, 2-methylthiophene on alkylation with MeI/AgClO₄ gave the trimeric product 3 instead of the anticipated 1,2-dimethylthiophenium perchlorate.

B. SPECTROSCOPIC PROPERTIES OF S-ALKYLATED THIOPHENES

1. Ultraviolet Spectroscopy

Any disruption of the ring current in the thiophene ring would be expected to produce significant changes in the ultraviolet (UV) spectra, and since the sulfur atom in S-alkylthiophenes is expected to be pyramidal, it may be inferred that severe disruption of ring current should be in evidence. Thus thiophene (Table II) exhibits a λ_{\max} at 231 nm in isooctane, whereas 1-methylthiophenium hexafluorophosphate exhibits two maxima at 220 and 267 nm

TABLE II
ULTRAVIOLET SPECTRA OF SIMPLE THIOPHENES AND THEIR
1-METHYLTHIOPHENIUM HEXAFLUOROPHOSPHATE SALTS^{a,b}

Ring substituent	Thiophene	Salt
None	231 (0.71)	220 (0.21), 267 (0.07)
2-Methyl	234 (0.76)	209, 227
3-Methyl	234 (0.53)	220 (0.28), 278 (0.12)
2,5-Dimethyl	236 (0.76)	209 (0.25), 285 (0.25)
2,5-Dimethyl ^c	236 (0.76)	214 (0.28), 288 (0.18)
2-Ethyl	234 (0.83)	278

^a Data from Acheson and Harrison (70JCS(C)1764).

^b Values given for λ_{\max} in nm, with $10^{-4} \epsilon$ in parentheses. Spectra measured in isooctane for thiophenes and in water for their salts.

^c 1-Ethyl derivative.

in aqueous solution. Direct comparison between the spectra is precluded due to the low solubility of the salt in nonpolar solvents, but the differences are sufficient to permit diagnosis of S-alkylation of the thiophene ring.

2. Nuclear Magnetic Resonance Spectroscopy

^1H -NMR spectra of S-alkylthiophenium salts have been examined in detail (Table III). Generally, small differences in the chemical shift of the ring protons are observed (relative to the parent thiophene derivatives), but since solubilities usually preclude direct comparison of the spectra, any significance may be lost. The methyl group in S-methylthiophenium salts usually resonates in the range δ 3.0–3.4 ppm.

The only available ^{13}C data on S-methylated thiophenes are a direct comparison of the spectra of 2,3,4,5-tetramethylthiophene and 1,2,3,4,5-pentamethylthiophenium fluorosulfonate (74TL75). In the case of the free thiophene, resonances were observed at δ 11.8 (2- and 5-methyl groups), 11.6 (3- and 4-methyl groups), 127 (α -ring carbon), and 132.4 (β -ring carbon) ppm. The salt shows equivalent resonances at 10.0, 12.8, 128.4, and 148.5 ppm [from tetramethylsilane (TMS) as an external standard], with the S-methyl carbon atom resonating at 26.0 ppm. Intuitively, the large chemical shift difference for the β -carbon atoms would be expected and may prove diagnostic.

3. Mass Spectroscopy

The mass spectra of S-alkylated thiophenium salts show a characteristic loss of the alkyl group from sulfur, with the result that the spectra appear similar to those of the parent thiophenes. Masses higher than those observed for the parent thiophene rarely corresponded to a molecular ion. In such cases, loss of a hydrogen atom occurred in both methyl and ethyl salts to give an $[\text{M} - 1]^{++}$ peak, which (when observable) was only of low intensity. Two structures, 4 or 5 have been proposed for this ion. In the case of the S-ethyl salts, further loss of a methyl group may give rise to an $[\text{M} - 16]^{++}$ peak and the thiapyrylium structure (6) has been advanced for this species.

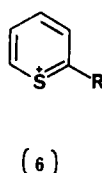
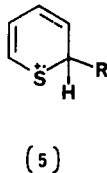
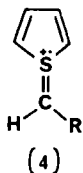
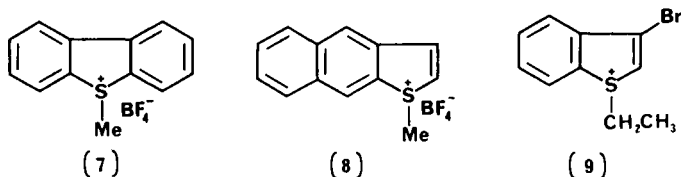


TABLE III
PROTON CHEMICAL SHIFTS IN S-ALKYLTHIOPHENIUM SALTS

Compound	Chemical shift δ				Other resonances	Solvent
	2H	3H	4H	5H		
Thiophene	7.00	7.20	7.20	7.00	—	CDCl ₃
1-Methylthiophenium hexafluorophosphate	7.53	7.53	7.53	7.53	S-CH ₃ , 3.11	CD ₃ CN
3-Methylthiophene	6.85	—	6.95	7.15	3-CH ₃ , 2.4	CDCl ₃
1,3-Dimethylthiophenium hexafluorophosphate	7.08	—	7.36	7.53	3-CH ₃ , 2.39; S-CH ₃ , 3.21	CD ₂ Cl ₂
1,2,5-Trimethylthiophenium hexafluorophosphate	—	6.98	6.98	—	2,5-CH ₃ , 2.48; S-CH ₃ , 3.21	CD ₂ Cl ₂
1-Ethyl-2,5-dimethylthiophenium hexafluorophosphate	—	7.05	7.05	—	2,5-CH ₃ , 2.45; S-CH ₂ , 2.93	CD ₂ Cl ₂
1-Methyl-2-phenethylthiophenium hexafluorophosphate	—	6.8–7.25	7.3	7.46	—CH ₂ CH ₂ —, 2.8–3.0; S-CH ₃ , 3.08; Ar—H, 6.8–7.25	CD ₂ Cl ₂

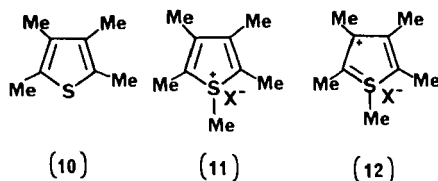
C. STRUCTURE OF S-ALKYLTHIOPHENIUM SALTS

No structural data are available for **2**, however, X-ray crystal structures have been determined for *S*-methylthiophenium tetrafluoroborate (**7**) and for 1-methylnaphtho[3,2-*b*]thiophenium tetrafluoroborate (**8**) and in both cases the sulfur atom is pyramidal (81JA289). Thus, the bond angle between the plane of the rings and the S-methyl group is 68.9° for **7** and 68.2° for **8**. By inference, the geometry in **2** should be similar.



¹H-NMR studies on **9** have shown that the methylene protons of the S-ethyl group appear as a 12-line multiplet and this is consistent only with these protons being diastereotopic, which is in turn dependent upon a pyramidal geometry at the sulfur atom. The calculated inversion barrier in the *S*-methylthiophenium cation (e.g., **2**) is on the order of 33 kcal mol⁻¹, which suggests that these salts should be configurationally stable at ambient temperature (84CC859). Although *S*-ethylthiophenium salts have been prepared (70JCS(C)1764), all of the known examples lack the necessary asymmetry that would render them amenable to study by NMR methods.

The pyramidal geometry at sulfur implies *sp*³ hybridization, and since aromaticity is formally dependent on *sp*² hybridization, a reduction in aromatic stabilization would be expected. This could, in principle, be offset by the use of *d* orbitals in hybridization/bonding, but such *d*-orbital participation is difficult if not impossible to quantify. It has been claimed (70JCS(C)1764; 74TL75) that both ¹³C- and ¹H-NMR data support *dπ*-*pπ* bonding. In particular, the large chemical shift difference between the β-carbon resonances in **10** and **11** (X = FSO₃) have been attributed to resonance contributions (such as **12**). Comparison of the chemical shift differences between ring protons in simple thiophenes and their *S*-alkylated derivatives (Table III) reveals a greater deshielding of the β protons than observed for the α protons. Similar observations have been made with the benzo[*b*]thiophenium salts.

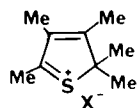


D. REACTIONS OF S-ALKYLTHIOPHENIUM SALTS

The structural similarities between S-alkylthiophenium salts and thiophene sulfoxides have prompted the suggestion that both classes are antiaromatic (70JA7610, 70JCS(C)1764). Thiophene sulfoxides are exceptionally reactive, undergoing spontaneous Diels–Alder dimerization unless stabilized by bulky substituents at the 2- and 5-positions. This type of reactivity is reminiscent of cyclobutadiene. In stark contrast to the sulfoxides, S-alkylthiophenium salts show no tendency to take part in Diels–Alder reactions either in an intra- or intermolecular sense. Pentamethylthiophenium hexafluorophosphate (**11**, $X = \text{PF}_6^-$) was shown to be completely unreactive toward both electron-rich and electron-deficient dienophiles under conditions where thiophene sulfoxides undergo efficient cycloaddition reactions.

The general stability of S-alkylthiophenium salts seems to be directly related to their alkylating properties, and even species that are conventionally regarded as poor nucleophiles are readily alkylated. Thus, dimethyl sulfoxide is methylated on oxygen at room temperature; alcohols react to yield the corresponding ethers, and relatively unreactive heterocyclic bases such as acridine are methylated at room temperature. This high reactivity is not unexpected since nucleophilic attack at the methyl group in S-methylthiophenium salts results in the loss of thiophene as a leaving group with the ring effectively regaining its aromaticity on cleavage of the carbon–sulfur bond.

The only other report on the reactivity of S-alkylthiophenium salts is seen in the observation that photolysis of **11** ($X = \text{FSO}_3^-$) in solution results in the migration of the S-methyl substituent to the α -position of the ring yielding the salt **13** ($X = \text{FSO}_3^-$), whose structure was determined by ^{13}C - and ^1H -NMR spectroscopy. This product, like the salt from which it was derived, proved to be very reactive and all attempts to isolate stable derivatives failed.

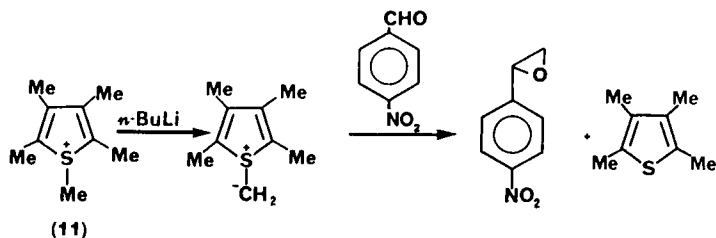


(13)

III. Thiophene S,C-Ylids

A. INTRODUCTION

Sulfur ylids have traditionally been prepared by two principal methods: (1) deprotonation of S-alkylsulfonium salts and (2) reaction of carbenes or carbenoids with thioethers (75MI1). Both methods have been applied to the



SCHEME 1

synthesis of thiophenium ylids, although the former method would appear to be of limited value due to the paucity of general methods of preparing S-alkylthiophenium salts. Deprotonation of the salt **11** (Scheme 1) with butyllithium at -45°C resulted in the formation of the intermediate ylid, which behaved as a typical sulfur ylid in its reaction with *p*-nitrobenzaldehyde to yield the epoxide (73TL3929). Aside from this isolated reaction, no other attempts to generate thiophenium ylids by deprotonation of S-alkylthiophenium salts have appeared.

The first reference to the formation of thiophenium ylids by carbene addition to thiophene appeared in 1972, when Durr and co-workers noted that pyrolysis of diazotetraphenylcyclopentadiene in thiophene resulted in a low yield of the ylid **14**, although no information on the yield of the reaction or the physical or spectroscopic properties of **14** were given (72TL1257).

These two reports clearly demonstrate that thiophene can form ylids, despite the considerably reduced nucleophilicity of the sulfur atom and that stable thiophenium ylids might be found. This was subsequently confirmed with the observation that the photolysis of dimethyl diazomalonate in thiophene result in the formation of **15**, which was isolated in low yield as a stable crystalline solid (77JOC3365). It was subsequently demonstrated by my own group that thiophenium bis(alkoxycarbonyl)methylides could be formed in high yield using rhodium(II) acetate-catalyzed addition of diazomalonate

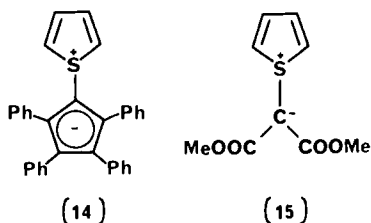
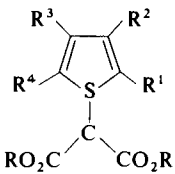


TABLE IV
THIOPHENIUM YLIDS

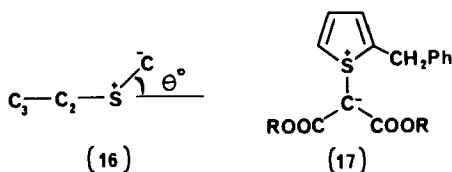
					
R	R ¹	R ²	R ³	R ⁴	Yield (%)
CH ₃	H	H	H	H	95
CH ₃ CH ₂	H	H	H	H	90
(CH ₃) ₃ C	H	H	H	H	80
CH ₃	Cl	H	H	Cl	100
CH ₃ CH ₂	Cl	H	H	Cl	60
CH ₃	CH ₂ OH	H	H	H	54
CH ₃	CH ₃	H	H	H	90
CH ₃	Br	H	H	H	73
CH ₃	Br	CH ₃	H	H	86
CH ₃	Br	H	H	Br	55
CH ₃	H	—CH=CH—CH=CH—		H	97
(CH ₃) ₃ C	CH ₃	H	H	H	92
(CH ₃) ₃ C	CH ₃ CH ₂	H	H	H	80
(CH ₃) ₃ C	(CH ₃) ₂ CH	H	H	H	78
(CH ₃) ₃ C	Cl	H	H	H	42
(CH ₃) ₃ C	Br	H	H	H	87
(CH ₃) ₃ C	I	H	H	H	75
(CH ₃) ₃ C	CH ₂ Ph	H	H	CH ₃	44
(CH ₃) ₃ C	CH ₂ Ph	H	H	CH ₃ CH ₂	75
(CH ₃) ₃ C	CH ₂ Ph	H	H	(CH ₃) ₂ CH	56
(CH ₃) ₃ C	CH ₂ Ph	H	H	Cl	51
(CH ₃) ₃ C	CH ₂ Ph	H	H	Br	49
(CH ₃) ₃ C	CH ₂ Ph	H	H	I	67
CH ₃	Cl	Cl	Cl	Cl	75

esters to thiophene derivatives. A large number of the bis(alkoxycarbonyl)-methylides (Table IV) have been prepared by this route (78CC83).

A detailed analysis of the reaction of diazoalkanes and α -diazocarbonyl compounds with thiophene has revealed that the formation of stable ylids is observed only with diazomalonic esters (79JCS(P1)2624). Other α -diazocarbonyl compounds, such as diazoacetic esters, Meldrum's diazo, or ethyl diazoacetoacetate, do not generally give rise to stable ylids. However, with tetrachlorothiophene under favorable conditions, the corresponding ylids may be isolated (84CC190).

B. STRUCTURE AND BONDING IN THIOPHENE S,C-YLIDS

In contrast to the S-alkylthiophenium salts, for which the structure and bonding considerations are based on analogies with the benzo-fused systems, more structural data are available for thiophenium ylids (78CC83). An X-ray crystal structure determination of thiophenium bis(methoxycarbonyl)-methylide has been carried out and accurate bond lengths and bond angles are available (Fig. 1). The sulfur atom in the ylid is unequivocally pyramidal, although the angle θ (16) between the plane of the ring and the ylid-carbon atom is 49.7° , which is significantly less than in the corresponding sulfonium salts and sulfoxides. The ylid sulfur-carbon bond [S—C(6)], not unexpectedly, is shorter than, for example, the carbon-sulfur bond in thiophene (70AX(B)1010). In addition, it appears that there is greater bond localization within the ring, as evidenced by the shortening of the C(2)—C(3) and C(4)—C(5) bonds relative to thiophene.



Confirmatory evidence for the pyramidal nature of the sulfur atom in the ylids is available from solution studies (84CC859) on the ylid 17. Thus, 17 ($R = t\text{-Bu}$) contains a prochiral benzyl groups, and, in the presence of the pyramidal sulfur atom, the benzylic protons are diastereotopic. Their

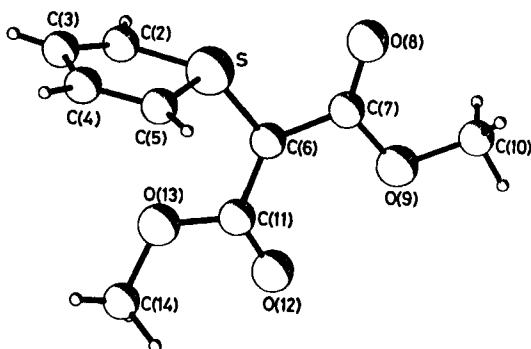


FIG. 1. The structure of the ylide. Bond lengths (Å): S—C(2), 1.745(7); S—C(5), 1.743(4); S—C(6), 1.711(4); C(2)—C(3), 1.326(6); C(3)—C(4), 1.439(10); C(4)—C(5), 1.320(8); C(6)—C(7), 1.441(6); C(6)—C(11), 1.431(6). Bond angles (degrees): C(2)—S—C(5), $92.2(3)$; C(2)—S—C(6), $116.8(2)$; C(5)—S—C(6), $114.7(2)$. Reprinted from Gillespie *et al.* (78CC83).

appearance as an AB quartet in the ^1H -NMR spectrum serves as a probe for inversion at the sulfur atom, whereas the ester groups, which also show non-equivalence in the ^1H -NMR spectrum, may serve as a probe for inversion at sulfur and/or rotation about the ylidic S—C bond. Lineshape analysis (68JA4854) of the benzylic AB spin system at 250 MHz of **17** ($R = t\text{-Bu}$) resulted in the activation parameters $\Delta G_{298}^\ddagger = 12.3 \text{ kcal mol}^{-1}$, $\Delta H^\ddagger = 17.2 \text{ kcal mol}^{-1}$, and $\Delta S^\ddagger = 15.5 \text{ cal mol}^{-1} \text{ K}^{-1}$. A similar study of the methyl ester (**17**, $R = \text{Me}$) gave comparable but less accurate results due to some overlap of the benzylic methylene and ester-methyl resonances. The free energies of activation for inversion at sulfur obtained in these measurements are significantly lower than those measured for the sulfoxide (**1**) (70JA7610).

This confirmation of the pyramidal nature of the sulfur atom and of the increased localization of the double bonds in the thiophene ring of the ylids poses some problems concerning their apparent stability, particularly in view of the known reactivity of the isoelectronic sulfoxides and sulfilimines (84CC190). A deshielding of ring protons in the NMR spectrum is generally considered to be diagnostic of ring current in aromatic systems and any significant change in ring current should result in an unfield shift of the ring-proton resonances. However, no obvious trend is evident with the thiophenium bis-(alkoxycarbonyl)methylides. The available proton NMR data show that the chemical shift values for the α - and β -ring protons in thiophene and thiophenium bis(methoxycarbonyl)methylide are virtually identical at δ 7.0 and 7.2 ppm, respectively. Further complications have arisen in an attempt to utilize proton chemical shift values in this way. Thus, contrary to prediction, the ring protons in 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide are deshielded by 0.2 ppm relative to 2,5-dichlorothiophene.

Initial studies on the variable-temperature ^1H - and ^{13}C -NMR spectra of the thiophenium bis(methoxycarbonyl)methylides revealed two temperature-dependent processes (85TH1). Initially the process with the higher free energy of activation (85HC(a)) was attributed to restricted rotation about the ylidic sulfur-carbon bond. But in light of more recent studies (84CC859), inversion at sulfur seems the most probable candidate, particularly in view of the fact that ΔG^\ddagger values in the range 11.2–14.8 kcal mol^{-1} were obtained, in broad agreement with the value obtained for **17** ($R = \text{CH}_3$). The second process showed a remarkably consistent free energy of activation over a range of compounds with $\Delta G^\ddagger \simeq 8.8 \text{ kcal mol}^{-1}$. This barrier has been attributed to hindered rotation about the ester carbon-oxygen bond, although a number of interesting questions about this barrier remain unanswered and await further study.

The ^{13}C -NMR spectrum of thiophene shows two resonances at 124.9 and 126.7 ppm against TMS, corresponding to the α - and β -ring carbon atoms. In thiophenium bis(methoxycarbonyl)methylide these resonances are shifted to

131.01 and 133.64 ppm, respectively. This corresponds to a deshielding of the α -carbon atom by 6.11 ppm and the β -carbon atom by 6.94 ppm; these figures, which are broadly similar, shed little light on the apparent anomalous stability of the ylids.

The most convincing evidence concerning the relative stabilities of thiophene S,C-ylids, S,N-ylids, and the sulfoxides comes from *ab initio* restricted Hartree–Foch molecular orbital (MO) calculations, in which the molecular parameters of the ylid **18** and the S-methyl thiophenium salt **19** were compared (84CC859). The ylid (**18**) has never been isolated, nor would one intuitively expect it to enjoy any real stability. However, it was chosen to simplify the MO calculations. The stability of ylids such as **14** and **15** is almost certainly due to the ability of these systems to delocalize the formal negative charge over several atoms, and clearly this facility is not present in **18**. Thus, **18** represents a highly localized ylidic structure. In principle, the salt **19** can be

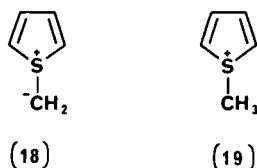


TABLE V
CALCULATED *ab initio* PROPERTIES OF **18** AND **19**^a

	18	19
$E_{\text{tot}}^{b,c}$ (a.u.), ground state ^d	−140.364	−140.471
$r_{\text{C-S}}^d$ (picometers)	160.4	181.4
E_{rel}^e , transition state ^f	13.15	32.74
E_{rel}^e , transition state ^g	27.00	
$r_{\text{C-S}}^d$ (picometers)	170	
E_{rel}^e , transition state ^h		27.00

^a Data reprinted from Bowles *et al.* (84CC859) with permission of the publisher.

^b 1 a.u. = 627.73 kcal mol^{−1}.

^c Obtained using an STO 3-21G basis set.

^d Molecular geometries were initially optimized using the MNDO SCF MO method (84CC859).

^e Energy to the ground state in kcal mol^{−1}.

^f Transition state for sulfur inversion.

^g Transition state for carbon–sulfur rotation with the carbon lone pair cis to the thiophene ring.

^h Transition state for carbon–sulfur bond rotation with the carbon lone pair trans to the thiophene ring.

considered as an extreme form of the ylid, in which delocalization is complete, and it was considered that the activation parameters determined for **17** should fall within the values calculated for **18** and **19**. These assumptions are adequately borne out (Table V), in that ΔH^\ddagger for inversion at sulfur in **18** is calculated to be $13.1 \text{ kcal mol}^{-1}$, whereas that for **19** is significantly higher at $32.6 \text{ kcal mol}^{-1}$ and the value determined for **17** ($R = \text{CH}_3$) is $16.8 \text{ kcal mol}^{-1}$.

Inspection of the calculated canonical molecular orbitals derived, using the same STO 3-21G basis set, for thiophene, thiophene 1-oxide, and **18** (Fig. 2a-c) show that, in the case of the ylid, significant conjugation of the ring π -electron system with the lone pair of electrons on sulfur is still possible, accounting for the similarity in aromaticity of thiophene and the S,C-ylids. In contrast, the closest equivalent MO in thiophene 1-oxide (Fig. 2c) is not significantly conjugated with the π -electron system of the ring, thus accounting for the pronounced difference in reactivity of the two isoelectronic systems. It is also of interest to note that the recently discovered thiophene S,N-ylids (*vide infra*) more closely resemble the sulfoxides than the S,C-ylids (Fig. 2d).

C. REACTIONS OF THIOPHENE S,C-YLIDS

1. Introduction

There can now be little doubt that the reaction of singlet carbenes and carbenoids with thiophene proceeds by attack of the carbene at the ring sulfur atom to generate the S,C-ylid. However, only in the special cases indicated above do these ylids enjoy any real stability. In the majority of cases, other products usually result from rearrangement of the intermediate ylids and the nature of the products formed is remarkably sensitive to both steric and electronic effects. Broadly speaking, six major reaction pathways have been observed: (1) 2-substituted thiophene formation, (2) 2*H*-thiopyran formation, (3) formation of derivatives of 2-thiabicyclo[3.1.0]hex-3-ene, (4) 3-substituted thiophene formation, (5) oxathiocin formation, and (6) carbenic fragmentation.

In addition to these reactions, which formally involve unimolecular reactions, it is also been reported (84CC190) that certain ylids derived from tetrachlorothiophene will undergo cycloaddition reactions.

Frequently, two or more of the product types are observed under the same reaction conditions, suggesting an extremely complex potential energy surface with many local minima. This, of course, means that it is impractical to consider the formation of each product type independently since small changes in substitution of the thiophene ring, or the carbene precursor, can bring about changes in product distribution. In addition, the temperature at

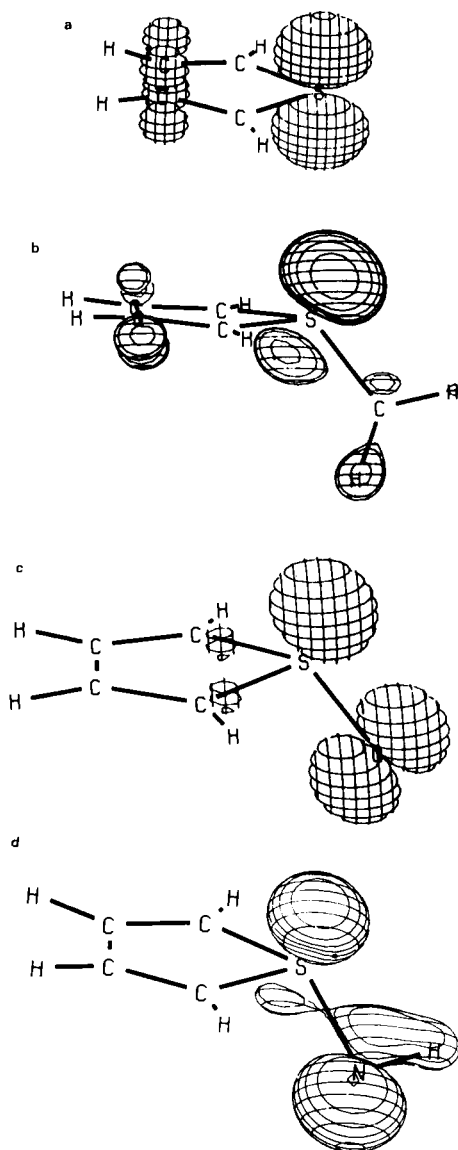
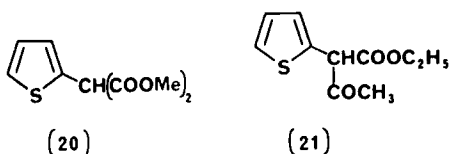


FIG. 2. Wavefunctions corresponding to the highest occupied molecular orbitals (HOMOs) of thiophene(a), a thiophene S,C-ylid (b), thiophene 1-oxide (c), and a thiophene S,N-ylid (d). [Figure 2a-c reprinted from Bowles *et al.* (84CC859).]

which the reaction is carried out, or the solvents employed, can also have a pronounced effect on the products of the reaction.

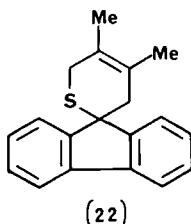
2. 2-Substituted Thiophene Formation

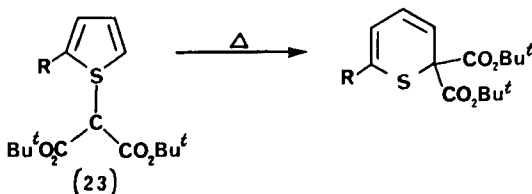
In a study of the reaction of thiophene with dimethyl diazomalonate, it has been observed that when copper(II) salts are used to bring about carbenoid formation, then the reaction was impractically slow, even at the temperature of refluxing thiophene. Dimethyl 2-(2'-thienyl)malonate (**20**) was formed in low yield as the only observable product (79JCS(P1)2624). When rhodium(II) salts were used as catalysts, the reaction occurred at room temperature, and the ylid (**15**) was formed in high yield. Subsequently it was demonstrated that thermolysis of **15** results in rearrangement to **20**, and the available evidence indicated that the rearrangement was intramolecular, involving a "walk" of the ylidic carbon atom to C-2 of the ring, followed by proton transfer (78CC85). In the case of ethyl diazoacetate, ethyl 2-(2'-thienyl)-3-oxobutanoate (**21**) is isolated directly under similar reaction conditions, and although intermediacy of the ylid is probable, it is insufficiently stable to be isolated. Similar results were also observed with diazoacetophenone.



3. 2H-Thiopyran Formation

Rearrangement of 2H-thiopyrans to thiophene derivatives is well documented, due largely to the studies of Brandsma and co-workers (69RTC30, 69RTC597, 69RTC732). It has also been demonstrated that dihydro-2H-thiopyrans (e.g., **22**) yield thiophene derivatives on pyrolysis and it has been





SCHEME 2

suggested that oxidation of the dihydro-2*H*-thiopyrans to the corresponding 2*H*-thiopyrans may precede the rearrangement (65TL3361; 80LA1604). However, it is relatively recently that the formation of 2*H*-thiopyrans during the rearrangement of thiophenium ylids has been reported (85CC1590). On heating thiophenium bis(*t*-butoxycarbonyl)methylides (**23**) at 110°C for short contact times, 2*H*-thiopyrans are formed in good yield (Scheme 2).

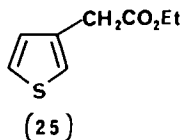
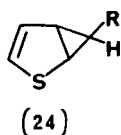
The structures of the 2*H*-thiopyrans formed in these reactions have been confirmed crystallographically. In these reactions it is evident that the 2*H*-thiopyrans are kinetic products since continued heating results in complete conversion to 2-substituted thiophenes. The ease with which the ylids rearrange to the 2*H*-thiopyrans is particularly sensitive to substituent effects. Thus, the 2-phenoxyethyl ylid (**23**, R = CH₂OPh) rearranges to the corresponding 2*H*-thiopyran during recrystallization from methylcyclohexane (88JCS(P1)803).

4. 2-Thiabicyclo[3.1.0]hex-3-ene Formation

Formally, the insertion of a carbene(oid) into the 2,3-double bond of the thiophene ring should result in the formation of the 2-thiabicyclo[3.1.0]hex-3-ene ring system. Copper(II)-catalyzed reaction of thiophene with diazomethane results in the formation of **24** (R = H) in modest yield (63TL1047). Analogously, the reaction of thiophene with ethyl diazoacetate yields **24** (R = CO₂Et) (22LA154). Although these reactions appear to be simple carbene insertion reactions, it is probable that this simple mechanism is not in operation. Rather, the cyclopropane derivatives **24** probably result from the initial formation of the ylid (e.g., **18**), which subsequently rearranges.

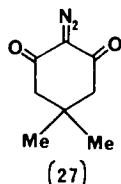
5. 3-Substituted Thiophene Formation

The only simple example of the formation of 3-substituted thiophene derivatives is the indirect acid-catalyzed rearrangement of **24** (R = CO₂Et) to give ethyl 2-(3'-thienyl)acetate (**25**) (22LA154). More complex examples of this reaction are discussed in Section III.D.

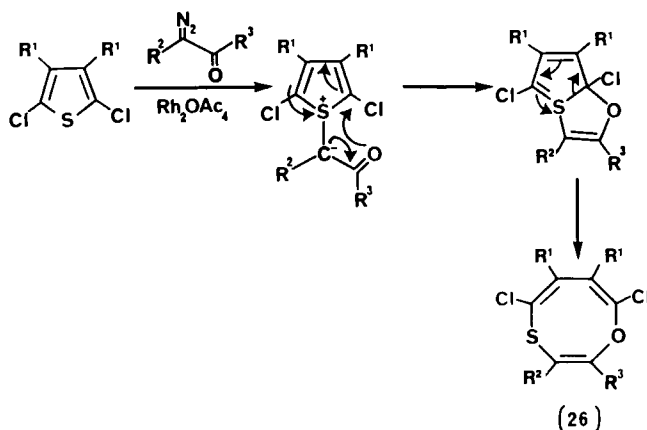


6. Oxathiocin Formation

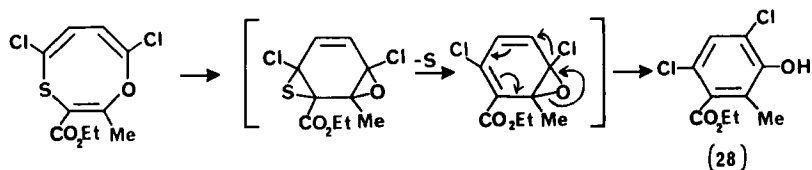
Oxathiocin formation occurs only in very special circumstances when the thiophene ring is substituted with chlorine at the 2- and 5-positions of the ring (88CC138). Reaction of ethyl diazoacetate with 2,5-dichlorothiophene under rhodium(II) acetate catalysis results in the formation of 2-methyl-3-ethoxycarbonyl-5,8-dichloro-1,4-oxathiocin (**26**, $R^1 = H$, $R^2 = CO_2Et$, $R^3 = CH_3$) (Scheme 3). In this reaction the intermediate ylid is not observed and the only isolated product is the oxathiocin. However, when diazodimedone (**27**) is used, the intermediate ylid has been isolated and



shown to undergo rearrangement to the oxathiocin in the temperature range 60–100°C. Above 110°C, the oxathiocins appear to be thermally labile and **26** ($R^1 = H$, $R^2 = CO_2Et$, $R^3 = CH_3$) undergoes sulfur extrusion and rearrangement to the phenol **28** (Scheme 4) (81T743).



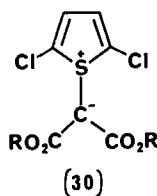
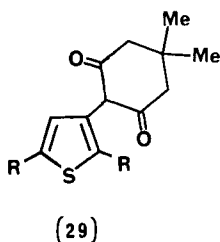
SCHEME 3



SCHEME 4

This thermal instability of oxathiocins is interesting in that formally this ring system is a 10π annulene, and as such it conforms to the Hückel $[4n + 2]$ rule. However it has been demonstrated crystallographically that the ring is nonplanar, precluding appreciable ring current. The migration of chlorine during this rearrangement (N.I.H. shift) is essential in order for the aromatization of the benzene ring to occur (Scheme 4) and must be exceptionally facile.

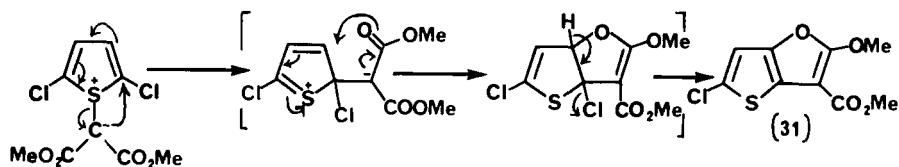
The unique role of the chlorine substituents in these reactions is underscored by the fact that 2,5-dimethylthiophene and 2,5-diiodothiophene react with, for example diazodimedone, to give the corresponding products of 3-substitution (29).



7. Carbenic Fragmentation

Carbenic fragmentation is formally the reverse of addition of carbenes to the sulfur atom of the thiophene ring, and has been observed only with 2,5-dichlorothiophenium bis(alkoxycarbonyl)methylides (30). When 30 ($R = \text{CH}_3$) is heated at 110°C in refluxing toluene in the presence of rhodium(II) acetate or copper(II) acetylacetonate, fragmentation of the ylid to 2,5-dichlorothiophene and the carbenoid occurs. The bis(methoxycarbonyl)-carbene has been trapped with alkenes to produce high yields of the cyclopropanated products (78CC641). Since the ylid is a stable crystalline solid with a long shelf life, it represents a convenient source of bis(methoxycarbonyl)carbene.

Bis(methoxycarbonyl)carbene generated in this way is a highly electrophilic species and readily reacts with mesomerically activated aromatic substrates to give the corresponding aryl malonates in fair to excellent yields,



SCHEME 5

as illustrated by the direct one-pot synthesis of dimethyl 2-(3'-indolyl) malonate in a yield of 85% with a reaction time of less than 5 min (79CC50). Although direct insertion into aliphatic C—H bonds has not been observed using this reagent, intermolecular insertion into N—H and O—H bonds seems facile. In addition, stereospecific deoxygenation of epoxides has been effected and in some instances the yields of this reaction are excellent (79TH1).

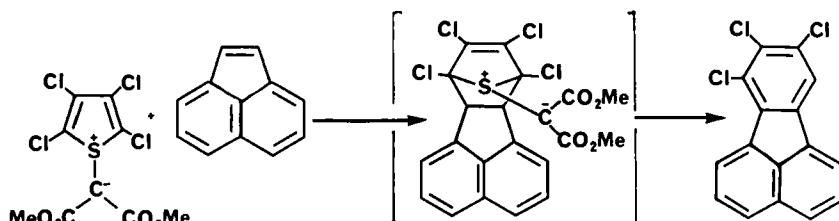
The effect of the chlorine atoms at the 2- and 5-positions of the thiophene ring appears to be crucial, and probably results in an inductive weakening of the ylidic sulfur—carbon bond. In the case of the 2,5-dibromo ylid, this type of fragmentation does not occur cleanly and there is evidence that other reactions, such as intramolecular rearrangements, are occurring under the reaction conditions. The presence of metal salts as catalysts for this fragmentation are essential since, in their absence, the ylid is stable at 110°C. At higher temperatures, an intramolecular rearrangement (Scheme 5) occurs with the formation of methyl 5-chloro-2-methoxythieno[3,2-*b*]furan-3-carboxylate (**31**) as the major product (79CC366).

8. Cycloaddition Reactions

Although thiophene 1-oxides, 1,1-dioxides, and S,N-ylids *vide infra* are known to undergo [4 + 2]-cycloaddition reactions, until recently no such reactions were known for the S,C-ylids. This is hardly surprising since so many low-energy reaction pathways are available for their rearrangement. However, Meth-Cohn and co-workers have shown that 2,3,4,5-tetrachlorothiophenium ylids react slowly with acenaphthylene to give adducts that undergo extrusion of the sulfur bridge (Scheme 6) followed by aromatization (86JCS(P1)233).

D. MECHANISM AND ENERGETICS OF THE FORMATION OF THE DIFFERENT PRODUCT TYPES

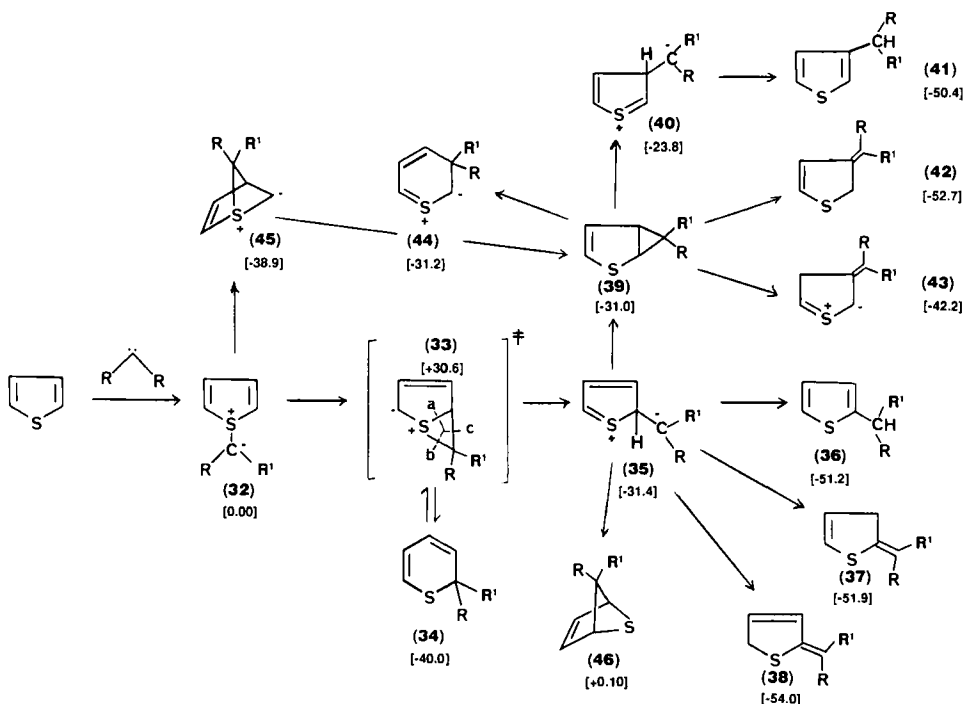
It seems probable that all of the product types observed in the reaction of carbenes with thiophene and its derivatives may be explained on the basis of



SCHEME 6

a single branching reaction pathway, in which the relative energies of the individual products are dictated by substituent effects (88JCS(P1)803), as outlined in Scheme 7. This scheme supposes that in all cases the first reaction between thiophene and the carbene gives rise to the ylid **32**, which under favorable conditions may be isolated (e.g., **32**, $R, R^1 = \text{cyclopentadienyl}$; or **32**, $R = R^1 = \text{CO}_2\text{Me}$).

In the majority of examples the ylids are insufficiently stable and further rearrangements occur. Attack at C-2 of the thiophene ring by the ylidic car-



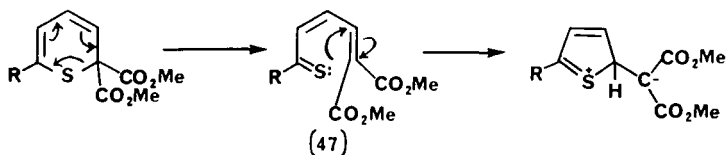
SCHEME 7. Numbers in brackets denote the calculated enthalpies of formation (in kcal mol⁻¹) relative to **32**.

bon atom should then result in the formation of the bicyclic ylid **33**, either as a formal intermediate or as one of three possible transition states leading to **32**, **34**, or **35**. Molecular orbital calculations have resulted in the location of only one stationary point for **33** ($R = R^1 = \text{CO}_2\text{H}$), corresponding to an energy maximum of $+30.6 \text{ kcal mol}^{-1}$ (relative to **32**, $R = R^1 = \text{CO}_2\text{H}$) (88JCS(P1)808). Confirmation of the existence of **33** ($R = R^1 = \text{CO}_2\text{H}$) as a transition state in this reaction is of interest, in that a similar type of phosphorus ylid has been proposed by Walker and co-workers (84CC1217) to rationalize the rearrangement of 1-fluoren-9-ylidene-1,2,5-triphenyl- λ^5 -phosphole.

Calculations on **33** ($R = R^1 = \text{CO}_2\text{H}$) reveal only one significantly weak bond corresponding to the formation/cleavage of the bond labeled c in Scheme 7. The transition state for a conventional 1,2-shift might be expected to have two weak bonds, one forming and the other cleaving, which indicates that **33** ($R = R^1 = \text{CO}_2\text{H}$) resembles more closely the transition state for the formation of a genuine bicyclic intermediate from **32** ($R = R^1 = \text{CO}_2\text{H}$). The failure to locate such an intermediate suggests that it must lie in a very shallow potential energy well.

Consideration **33** immediately suggests a route to the 2*H*-thiopyrans. Cleavage of bond a results in the formation of the 2*H*-thiopyran ring, whereas cleavage of bond b would result in the formation of the dipolar intermediate **35**. The experimental isolation of **34** ($R = R^1 = \text{CO}_2\text{Bu}'$) rather than **35** at relatively low temperatures suggests that if **33** ($R = R^1 = \text{CO}_2\text{Bu}'$) is indeed a common precursor to both products, then the barrier to the formation of **35** ($R = R^1 = \text{CO}_2\text{Bu}'$) must be higher than for **34** ($R = R^1 = \text{CO}_2\text{Bu}'$). In addition, the observation that **36** may be derived from **34** under conditions of thermodynamic control suggests either that cleavage a may occur reversibly, or that **34** may be converted to **35** by alternative mechanisms. An alternative mechanism (Scheme 8) involves an electrocyclic ring opening of the 2*H*-thiopyran to a thiocarbonyl compound, which could then cyclize by a Michael-type addition to produce the five-membered dipolar intermediate **35**. Although this mechanism appears to be attractive, experimentally there is little evidence to support it. Thus, when the 6-bromo-2*H*-thiopyran (Scheme 8) is subjected to rearrangement in alcoholic media, on ring opening, the intermediate thioacid bromide (**47**, $R = \text{Br}$) would be expected to be very reactive and result in thioester formation and subsequent reaction to yield a 2-alkoxythiophene derivative. Experimentally, however, no such reaction has been observed.

The dipolar intermediate **35** is pivotal in further reactions. The formation of **36** requires a 1,2-hydrogen shift and formally at least such a shift would be a thermally forbidden pericyclic reaction. An alternative to the forbidden process would involve a thermally allowed 1,5-shift to give, for example, **37**



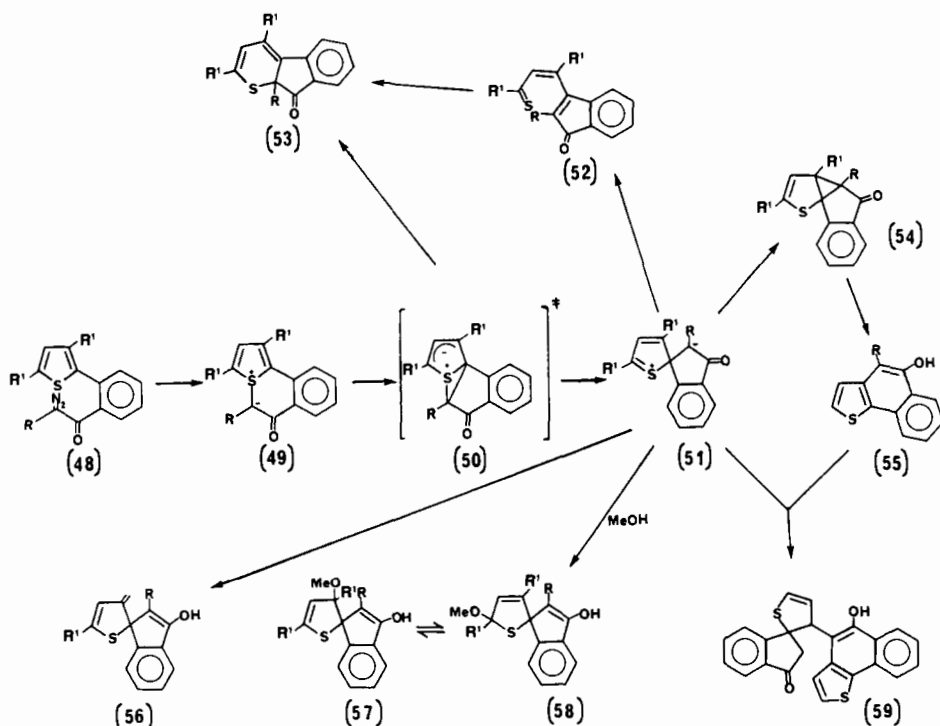
SCHEME 8

or **38**, whose calculated energies suggest that they are viable products. In solution, it is also quite possible that the hydrogen shift could be a result of a series of prototropic equilibria catalyzed by traces of acid or base.

The dipolar intermediate **35** may rearrange in several other ways. Ring closure to give the cyclopropane (**39**, $R = R^1 = \text{CO}_2\text{H}$) is calculated to proceed with an activation energy that is lower than for the formation of **36** ($R = R^1 = \text{CO}_2\text{H}$). However, when $R = \text{CO}_2\text{H}$ at least, **39** would not represent the thermodynamic product since it is calculated to be significantly less stable than **36** ($R = R^1 = \text{CO}_2\text{H}$), **37** ($R = R^1 = \text{CO}_2\text{H}$), or **38** ($R = R^1 = \text{CO}_2\text{H}$). It would therefore correspond to a kinetic product. A second pathway for the formation of **39** ($R = R^1 = \text{CO}_2\text{H}$) by the direct 1,3-migration of the bis(carboxy)methylene group by way of **45** ($R = R^1 = \text{CO}_2\text{H}$) might be envisaged. However, the calculated activation energy for this process is high ($+69.5 \text{ kcal mol}^{-1}$), effectively ruling out this possibility. The alternative ring closure to **46** ($R = R^1 = \text{CO}_2\text{H}$) by attack of the carbanionic center) with C-5 of the thiophene ring would also appear to be thermodynamically unfavorable.

Ring opening of the 2-thiabicyclo[3.1.0]hex-3-ene (**39**) to **40**, **42**, or **43** could in principle offer feasible routes to 3-substituted thiophene derivatives (**41**) and the relative energies of these structures support the possibility of their isolation. Indeed, although structures such as **37**, **38**, and **42** are not well known in the thiophene series, the corresponding furan analogs are well documented. An interesting point concerning the calculated energies of this reaction scheme is the prediction of the stability of such products and hitherto unknown structures such as **44**.

Further experimental support of these calculations is to be found in the excellent work of Skramstad and co-workers, who examined the fate of carbenoids with thiophenes in intramolecular reactions (84ACS(B)533). Thus, reaction of derivatives of the diazoketone **48** (Scheme 9) with rhodium(II) acetate provides an interesting range of compounds, dependent both on reaction conditions and substitution. In the case of **48** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$), the products **53** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$) and **55** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$) are formed and may be rationalized in terms of rearrangement of the initially formed ylid **49** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$) through **50** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$)



SCHEME 9

directly to **53** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$), although a mechanism involving the dipolar intermediate **51** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$) (cf. Scheme 7), followed by ring opening to the thiocarbonyl compound **52** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$), is the mechanism favored by Skramstad and co-workers (84CC208). The product **55** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$) formally corresponds to the direct formation of a 3-substituted thiophene and is probably derived by way of the intermediate 2-thiabicyclo[3.1.0]hex-3-ene derivative (**54**, $R = \text{CO}_2\text{Me}$, $R^1 = \text{H}$). When the diazo compound **48** ($R = R^1 = \text{H}$) was subjected to similar reaction conditions, the major product was **54** ($R = R^1 = \text{H}$). Acid-catalyzed rearrangement of **54** results in the formation of **55** ($R = R^1 = \text{H}$) and the dimer **59**, which is presumably formed by the reaction of **55** with **51**. When this reaction was carried out using methanol as a solvent, a mixture of the spiro compounds **57** ($R = R^1 = \text{H}$) and **58** ($R = R^1 = \text{H}$) resulted (86ACS(B)178).

Substitution of the thiophene ring with methyl groups **48** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{Me}$) produced an unexpected result in the formation of the spirodihydrothiophene **56** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{Me}$) (86ACS(B)303). This result is

particularly significant in that the analogous derivative **48** ($R = H$, $R^1 = CH_3$) resulted in the formation of **53** ($R = H$, $R^1 = Me$) and **54** ($R = H$, $R^1 = Me$) and offers further support for the intermediacy on **51**.

IV. Thiophene S,N-Ylids

A. INTRODUCTION

Sulfur–nitrogen ylids (sulfilimines or sulfilimides) are well known and may be generated by the reaction of azides with thioethers. These reactions formally involve the breakdown of the azides to nitrene intermediates, which then react with the sulfur atom of the thioethers. Until comparatively recently, no evidence for the existence of ylids in which the sulfur atom forms part of the thiophene ring had been advanced. Thiophene itself was shown to react with ethoxycarbonylnitrene to give pyrrole as the major product, and this reaction has been interpreted in terms of electrophilic attack at the 2 position of the thiophene ring, followed by a ring opening–ring closure sequence with subsequent elimination of sulfur (64TL2185).

B. SYNTHESIS OF THIOPHENE S,N-YLIDS

Recognizing the essential halophobicity of nitrenes, it was conceived by Meth-Cohn and co-workers that halothiophenes should prove better substrates in any attempt to generate thiophene S,N-ylids (84CC190). Decomposition of ethyl azidoformate in $130^\circ C$ in tetrachlorothiophene led to the formation of the ylid **60** ($R = CO_2Et$) in 44% yield. The related ylids **60** ($R = CO_2Ph$) and **60** ($R = SO_2C_6H_4Me^P$) were also prepared by a similar procedure, albeit in lower yield ($\approx 25\%$). Confirmation of the structure of **60** ($R = CO_2Et$) comes from a consideration of the spectral data, by hydrogenolysis of the sulfur–nitrogen bond over Raney nickel, and by an X-ray structure determination on **60** ($R = SO_2C_6H_4Me^P$) (84PC1).

To date, these three sulfur–nitrogen ylids are the only such structures to appear in the literature. It is particularly significant that 2,5-dichloro-, 2,5-dibromo-, and 2,3,4,5-tetrabromothiophenes all fail to give ylids under similar reaction conditions.

C. STRUCTURE OF THIOPHENE S,N-YLIDS

Although an X-ray crystal structure of **60** ($R = SO_2C_6H_4Me^P$) has been elucidated, the structural data for this compound are not generally available

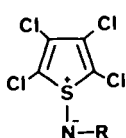
at the present time. However, as with the sulfoxides and the S,C-ylids, the sulfur atom is pyramidal. Molecular orbital calculations (Fig. 2d) show that the S,N-ylids should more closely resemble the sulfoxides than the S,C-ylids in their chemical reactivity, and this is borne out in practice.

D. REACTIONS OF THIOPHENE S,N-YLIDS

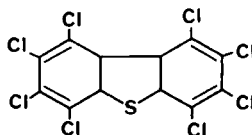
1. Sulfur–Nitrogen Bond Cleavage

Despite its apparent thermal stability, the S—N bond in **60** is readily cleaved. Hydrogenolysis of **60** ($R = \text{CO}_2\text{Et}$) using Raney nickel/hydrogen results in the formation of tetrachlorothiophene (61%) and ethyl carbamate (68%). Photolysis of **60** ($R = \text{CO}_2\text{Et}$) in cyclohexane solution using a medium pressure mercury lamp resulted in the formation of ethyl cyclohexylcarbamate in 85% yield; this product is clearly derived by insertion of a singlet nitrene derived from sulfur–nitrogen bond cleavage into a C—H bond of the cyclohexane ring (86JCS(P1)233).

This reaction should be seen in marked contrast to the more difficult photolysis of ethyl azidoformate, which requires low-wavelength light and quartz equipment, suggesting that the ylid is likely to prove a valuable precursor of the nitrene. The photolysis of **60** ($R = \text{CO}_2\text{Ph}$ or $\text{SO}_2\text{C}_6\text{H}_4\text{Me}^p$) proved them to be less efficient nitrene sources (87JCS(P1)1553).



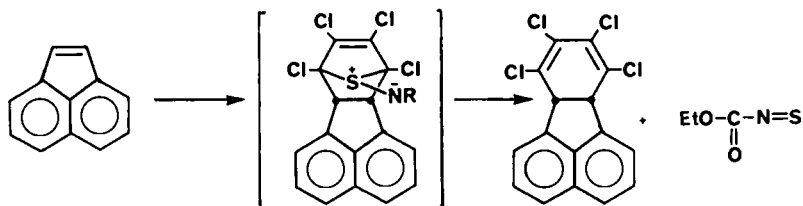
(60)



(61)

2. Cycloaddition Reactions

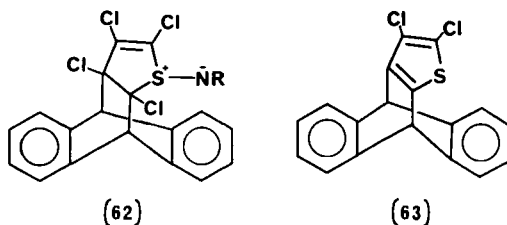
Thiophene 1-oxide is unusually reactive both as a diene and as a dienophile in the Diels–Alder reaction and thiophene S,N-ylids apparently exhibit similar reactivity. When electron-rich alkenes, (e.g., acenaphthalene) are treated with **60** ($R = \text{CO}_2\text{Et}$) (Scheme 10), a rapid reaction ensues to yield the product derived from a [4 + 2]-cycloaddition followed by cheletropic elimination of a thionitroso compound. This reaction appears to be fairly general for nonhindered alkenes, and even relatively unreactive systems, such as thiophene itself, give low yields of **61**. This is an unusual reaction



SCHEME 10

in view of the known lack of reactivity of thiophene under Diels–Alder conditions.

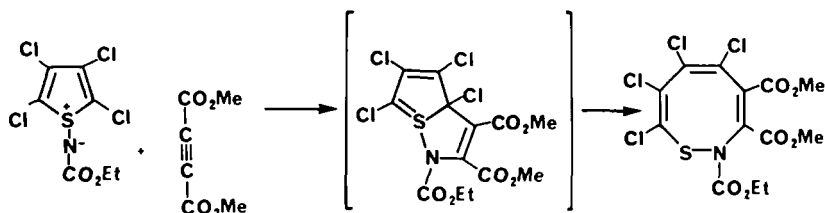
Thionitroso compounds are a highly reactive class of compounds and their intermediacy is usually inferred by trapping experiments (84CC1114). The cycloaddition/elimination sequence (Scheme 10) represents a particularly efficient route to these very reactive species which have been trapped in $[4 + 2]$ -cycloaddition reactions. In addition, the thionitroso compounds have been shown to exhibit unusually high reactivity in the ene reaction (86JCS(P1)245). As with thiophene sulfoxides and sulfones, the S,N -ylid **60** ($R = CO_2Et$) has also been shown to function as a dienophile in $[4 + 2]$ -cycloaddition reactions; with anthracene, the cycloadduct **62** ($R = CO_2Et$) is formed in 65% yield. Reduction of **62** with zinc in methanol gives the tryptidine analog **63**. Similar reactivity has been reported with a number of conjugated dienes.



Somewhat unusually, the ylid **60** ($R = CO_2Et$) has been shown to function as a six-membered system in its reaction with dimethyl acetylenedicarboxylate (Scheme 11), although it seems improbable that this is a concerted reaction.

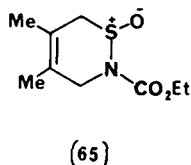
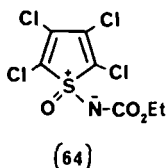
3. Oxidation of Thiophene S,N -Ylids

When the ethoxycarbonyl ylid **60** ($R = CO_2Et$) is treated with *m*-chloroperbenzoic acid, the sulfoxilimine **64** ($R = CO_2Et$) is formed in high yield.



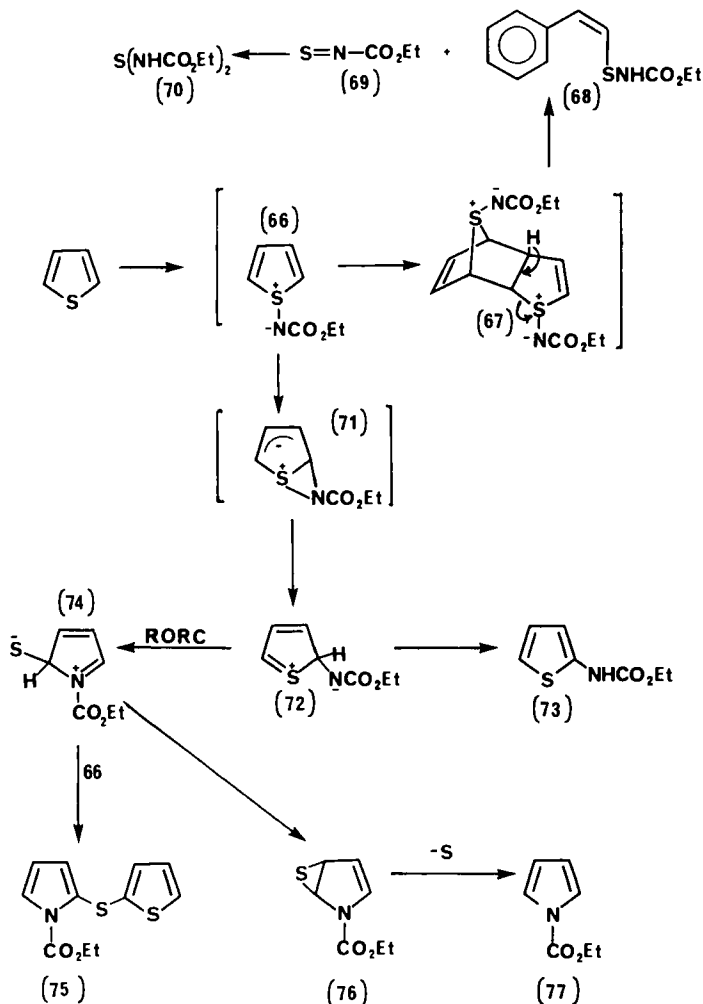
SCHEME 11

The latter compound is similar to **60** ($R = \text{CO}_2\text{Et}$) in reactivity toward acenaphthylene, undergoing $[4 + 2]$ -cycloaddition/cheletropic elimination to the known sulfinylamine $\text{EtO}_2\text{C}-\text{N}=\text{S}=\text{O}$, which was sufficiently stable to be isolated but underwent facile cycloaddition with 2,3-dimethyl-1,3-butadiene to give the thiazine sulfoxide **65**. Although **64** is a fairly reactive molecule, the reactivity in cycloaddition reactions is less than that of **60**, which is in keeping with the known differences in reactivity of thiophene 1-oxide and thiophene 1,1-dioxide.



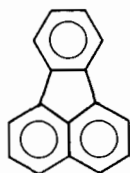
E. GENERAL CONSIDERATIONS ON THE REACTIONS OF NITRENES WITH THIOPHENE

In light of the known reactivity of the thiophene S,N-ylids, a detailed examination of the reaction of thiophene with ethyl azidoformate has been undertaken. A careful product analysis revealed the presence of previously unreported products, such as **68**, **70**, and **75**, which can be explained satisfactorily only in terms of the intermediacy of the thiophene S,N-ylid **66** (Scheme 12) (86TL1105). Thus, if the initial reaction of thiophene with the ethoxycarbonylnitrene generates **66**, the products **68–70** may be rationalized in terms of a Diels–Alder dimerization to **67**. Cheletropic elimination of **69** from **67**, followed by aromatization, would result in the formation of **68**. Alternatively, **66** could undergo rearrangement by way of a bicyclic transition state (**71**) (cf. **33**, Scheme 7) to a dipolar intermediate **72** (analogous to **35**, Scheme 7). Proton transfer in **72** would then furnish **73** analogous to the 2-

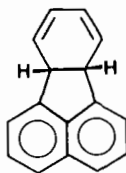


SCHEME 12

substitution products observed with the S,C-ylids. Ring opening of **72** followed by ring closure is expected to generate **74**, which goes on to give **77**, possibly by way of sulfur extrusion from the episulfide **76**. Reaction of **74** with the ylid **66**, followed by cleavage of the sulfur–nitrogen bond and proton transfer, could then furnish **75**. Evidence to support the intermediacy of the S,N-ylid **66** comes from trapping experiments using acenaphthylene, in which



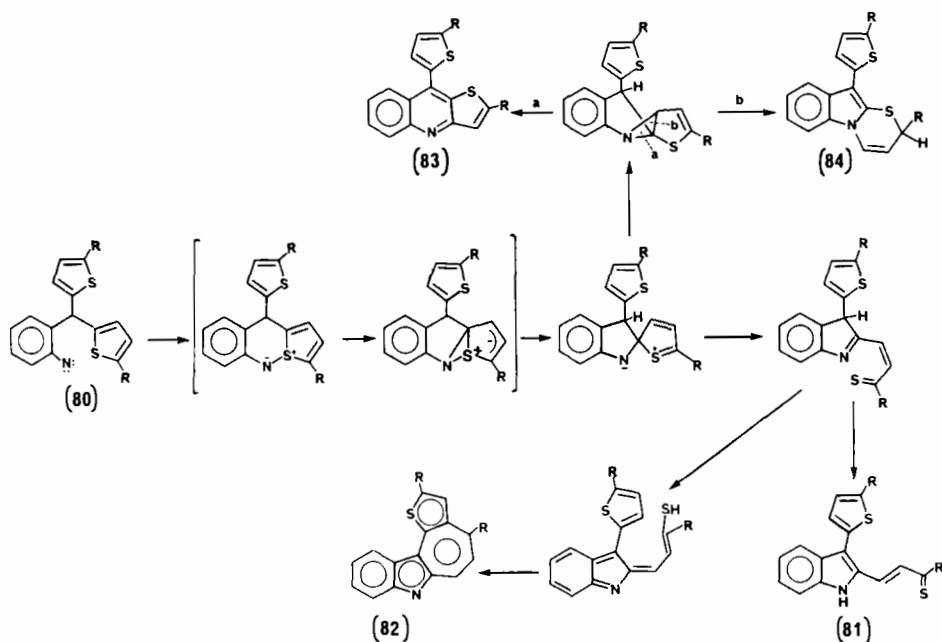
(78)



(79)

low yields of fluoranthene (78) and its 6b,10a-dihydro derivative (79) were isolated.

As in the case of the S,C-ylids, the results of intramolecular trapping of nitrenes support this general scheme (79TL1445). Thus, generation of the nitrene **80** resulted in the isolation of products **81–84** and formation of these products (Scheme 13) may be rationalized in terms of initial ylid formation, followed by rearrangement by routes entirely similar to those proposed in Scheme 12. The isolation of the thioketone **81** (80JCR(S)288) is particularly significant in view of the suggestion that such thiocarbonyl compounds might be intermediates in the rearrangement of the analogous S,C-ylids.



SCHEME 13

V. Conclusions

Barely 10 years has passed since a practical route to thiophene S,C-ylids was first developed, and less than 4 years since the analogous S,N-ylids first appeared. During this time, a thought-provoking diversity of chemistry has developed around these new families of ylid structures and many synthetic and mechanistic questions remain unanswered. The available evidence suggests that carbenes, nitrenes, and arynes (81CC124) attack the sulfur atom in the thiophene ring as a first step and this has prompted us and others to ask the question "do thiophenes tend to react at sulfur with all hard electrophiles?" If this is the case, then conceivably electrophilic acylation of thiophene may proceed by the initial attack of the acylium species at sulfur prior to migration to C-2 of the ring, and our classical ideas on electrophilic substitution of thiophenes might require revision. My own preliminary calculations indicate that attack at C-2 of the ring is thermodynamically favored relative to attack at the sulfur atom, but it is possible that attack at sulfur could be a kinetically controlled process.

It is to be hoped that the next 10 years provide some answers to these remaining questions.

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1,4-Diazocines

HOWARD D. PERLMUTTER

*Department of Chemical Engineering and Chemistry,
New Jersey Institute of Technology, Newark, New Jersey 07102*

I. Scope and Nomenclature	185
II. Preparative Methods	187
A. Via Ring Closure	187
1. Nucleophilic Displacement by Amines on Electrophilic Carbon	187
2. Cyclizations of Aminocarbonyl Compounds	187
3. Ring Closures Involving Carbon–Carbon Bond Formation	189
B. Via Ring Expansion or Contraction	190
1. Schmidt Reaction of Azacycloheptanones or Cyclohexanediones	190
2. Ring Opening of Three-Membered Rings (i.e., Azahomobenzenes)	192
3. Ring Opening of Diazabicyclo[3.3.0]octanes (e.g., Imidazoisindolones and Pyrroloimidazoles)	193
4. Ring Opening of Diazabicyclo[4.2.0]octanes	194
C. Via Condensations	196
1. Condensations between Dicarboxylic Acid Derivatives and 1,2-Diamines	196
2. Condensations of Diamines with Saturated Electrophilic Carbon	199
3. Condensations of Diamines with Aldehydes and Ketones	201
a. Synthesis of Biaryl Derivatives	201
b. The Controversial History of Dibenzo[<i>b,f</i>]-1,4-diazocines	202
4. "Mixed" and Other Condensations	206
III. Theoretical and Structural Studies	209
IV. Reactions	217
A. Eight-Membered Ring-Preserved Annulations	217
B. Eight-Membered Ring-Preserved Defunctionalizations, Functionalizations, Reductions, and Oxidations	218
C. Ring Contractions	219
D. Ring Expansions	222
E. Ring-Opening Reactions	222
V. Applications	223
References	224

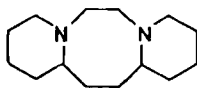
I. Scope and Nomenclature

This article covers eight-membered rings containing two nitrogens in a 1,4 position (**1**), and their fused-ring analogs. Excluded from coverage are (1) compounds in which *both* nitrogens form part of a fusion bond (e.g., **2**) and

(2) structures in which nonadjacent ring atoms are linked by a bridge (e.g., 3 and 4).



(1)



(2)



(3)



(4)

In some respects, the nomenclature of 1,4-diazocines is similar to that for the eight-membered ring containing one nitrogen (82AHC115). The completely unsaturated compound, for which there exists two valence tautomeric structures, 5 and 6, is called 1,4-diazocine. The partially saturated derivatives are prefixed dihydro-, tetrahydro-, etc. The totally saturated compound is called perhydro-1,4-diazocine, or 1,4-diazacyclooctane.

In this article, *all* compounds bearing two nitrogens in a 1,4 position are covered (except for the aforementioned exclusions), regardless of formal nomenclature. For example, benzo-2,5-diazocine (7) and benzo-1,6-diazocine (8) are both included.

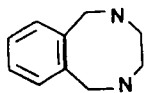
Certain abbreviations are used in the article for compounds that are mentioned repeatedly. Thus, ED is ethylenediamine, OPD is *o*-phenylenediamine, DMAD is dimethyl acetylene dicarboxylate, Bs is benzenesulfonyl, and Ts is *p*-toluenesulfonyl.



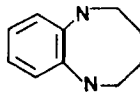
(5)



(6)



(7)



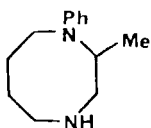
(8)

II. Preparative Methods

A. VIA RING CLOSURE

1. Nucleophilic Displacement by Amines on Electrophilic Carbon

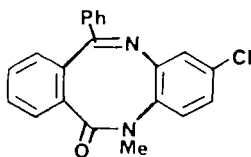
Reductive cyclization of *N*-(γ -chlorobutyl)-*N*-1-(cyanoethyl)aniline afforded diazocine **9** (64FRP1378964; 66USP3247206).



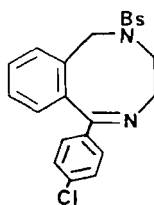
(9)

2. Cyclizations of Aminocarbonyl Compounds

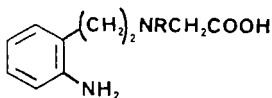
Topliss reductively cyclized *N*-(2-nitro-4-chlorophenyl)-*N*-methyl-2-benzoylbenzamide to dibenzo[*b,f*]-1,4-diazocine **10** (67JMC642; 68USP3409608). Cyclodehydration of *N*-(2-aminoethyl)-*N*-2-(4-chlorobenzoyl)benzylbenzenesulfonamide afforded tetrahydro-2,5-benzodiazocine **11** (67JOC3270; 70USP3496164). Cyclization of the diamino acids **12** using dicyclohexylcarbodiimide (DCC) resulted in formation of benzodiazocines **13**. Com-



(10)

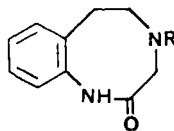


(11)



(12)

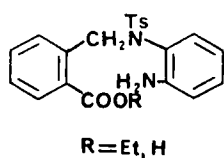
R = Me, Bs



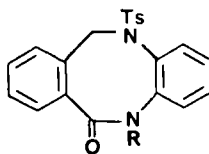
(13)

pound **13** ($R = \text{Me}$), but not **13** ($R = \text{SO}_2\text{Ph}$), could be reduced with lithium aluminum hydride to the 2-deoxo derivative (71CJC2023).

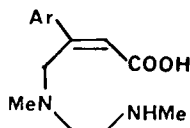
Saunders and Sprake cyclized the amino ester and acid **14** and obtained the dibenzo[*b,f*]-1,4-diazocine **15**. Dehydrosulfonation of **15** ($R = \text{alkyl}$) afforded ring-contracted products (see Section IV,C) (72JCS(P1)1964). Cyclization of the diamino acid **16** using DCC and triethylamine resulted in formation of 1,4-diazocinone **17**. This compound was also prepared by a ring-expansion route (see Section II,B,4) (74JOC1710).



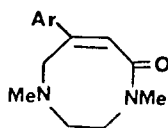
(14)



(15)

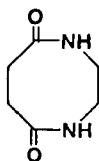


(16)



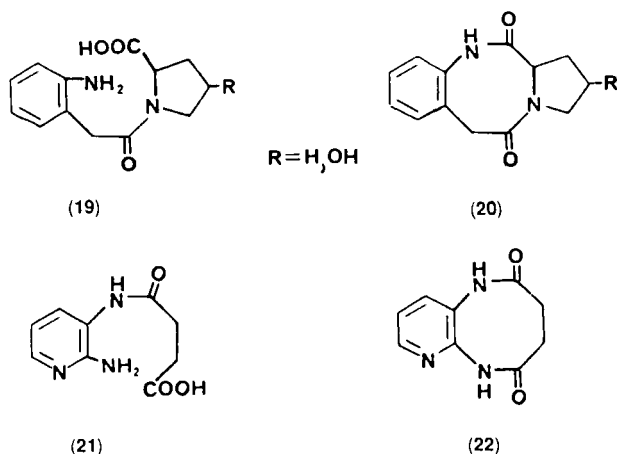
(17)

When *N*-succinylethylenediamine was heated above its melting point, the resulting dehydration afforded 1,4-diazocinedione **18**. This compound was also obtained by a condensation method (see Section II,C,1) (75JHC763).



(18)

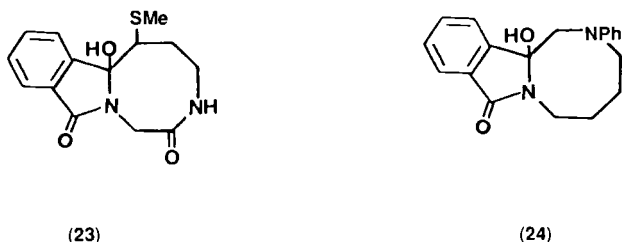
Massa *et al.* cyclized pyrrolidines **19** in DCC to obtain the pyrrolidino-1,4-benzodiazocinediones **20** (81FES425). When Thompson reacted succinic anhydride with 2,3-diaminopyridine, the diamino acid **21** was obtained. This compound could be cyclodehydrated to **22** in acetic anhydride; however, succinic and phthalic anhydride reacted with a diaminopyridine to afford diazocines directly (see Section II,C,1) (86JHC1545).

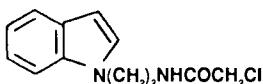


3. Ring Closures Involving Carbon–Carbon Bond Formation

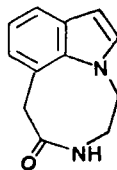
Kanaoka and co-workers have prepared isoindolo-1,4-diazocines by regioselective remote photocyclization of phthalimides with substituents R at nitrogen. When R was $\text{CH}_2\text{CON}(\text{CH}_2)_3\text{SCH}_3$, compound **23** was obtained along with a larger amount of a nine-membered ring containing endocyclic sulfur (74JAP74-102696; 76JA2349). When R was $(\text{CH}_2)_4\text{N}(\text{Me})\text{Ph}$, diazocine **24** was isolated, along with a smaller amount of an azepine containing exocyclic anilino nitrogen. This compound could be dehydrated to an unsaturated diazocine (82CPB1579). Photocyclization has also been employed by Naruto and Yonemitsu, who irradiated the N-substituted indole **25** and obtained **26**, in addition to an azepinoindole (80CPB900).

Acid-catalyzed cyclizations have been used to synthesize 1,4-diazocines. The benzilic acid amide **27** was converted into benzodiazocinone **28** (65KGS476). DeMartino *et al.* reported that treatment of **29** ($R = \text{NHAc}$, $R^1 = \text{H}$) and **29** ($R = \text{NHCOPh}$, $R^1 = \text{H}$) with phosphoryl chloride afforded





(25)

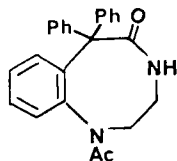


(26)

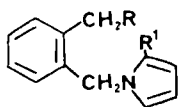
benzopyrrolodiazocine **30** ($R = \text{Me}$) and **30** ($R = \text{Ph}$), respectively. Vilsmeier–Hack formylation of **29** ($R = \text{NHAc}$, $R^1 = \text{H}$) at room temperature for 3 hr yielded **29** ($R = \text{NHAc}$, $R^1 = \text{CHO}$), which upon alkaline hydrolysis gave **30** ($R = \text{H}$). Vilsmeier–Hack formylation of **29** ($R = \text{NHAc}$, $R^1 = \text{H}$) at 120°C for 2 hr yielded **30** ($R = \text{H}$) directly. Alternatively, formylation of **29** ($R = \text{phthalimido}$, $R^1 = \text{H}$), followed by alkaline hydrolysis, gave **30** ($R = \text{H}$) in somewhat lower yield. Treatment of **29** ($R = \text{NH}_2$, $R^1 = \text{H}$) with ethylchloroformate followed by intramolecular cyclization of the product (**29**, $R = \text{NHCO}_2\text{Et}$, $R^1 = \text{H}$) afforded the analogous lactam, pyrrolobenzodiazocinone **29** ($\text{RR}^1 = \text{NHCO bridge}$) (72JCS(P1)2504).



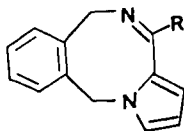
(27)



(28)



(29)



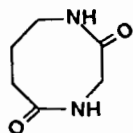
(30)

B. VIA RING EXPANSION OR CONTRACTION

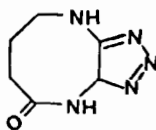
1. Schmidt Reaction of Azacycloheptanones or Cyclohexanediones

Sekiguchi reacted 1,3-cyclohexanedione with hydrazoic acid in the presence of sulfuric acid and obtained small amounts of bislactam **31** and triazolo derivative **32**, in addition to larger amounts of the correspond-

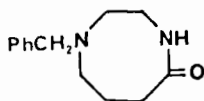
ing 1,5-diazocines. Compound **32** was believed to arise not from **31**, but from Schmidt reaction of a postulated intermediate, triazoloazepinone (65BSF691). Similar treatment of benzyl-1-azacycloheptane-4-one afforded compound **33** and a smaller amount of tetrazolo derivative **34** (71BCJ478). However, when Misiti *et al.* treated benzazepinone **35** and its N-tosyl derivative with sodium azide in the presence of concentrated sulfuric and glacial acetic acids, they obtained a small amount of the tetrazolodiazocines **36**. In addition, a 1,5-diazocine alkyl migration product was isolated (73JHC689). Kawamoto *et al.* ran a Schmidt reaction on **35** and obtained a small amount of 1,6-benzodiazocinone **37** (73BCJ3898). Toscano *et al.* ran a similar Schmidt reaction on isomeric compounds **38** and **39** and isolated isomeric 1,4-diazocinones **40** and **41**, respectively (76JHC475).



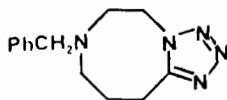
(31)



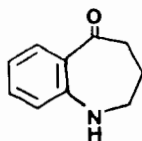
(32)



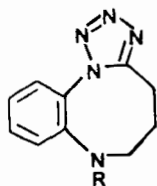
(33)



(34)

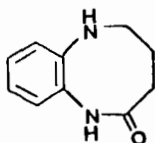


(35)

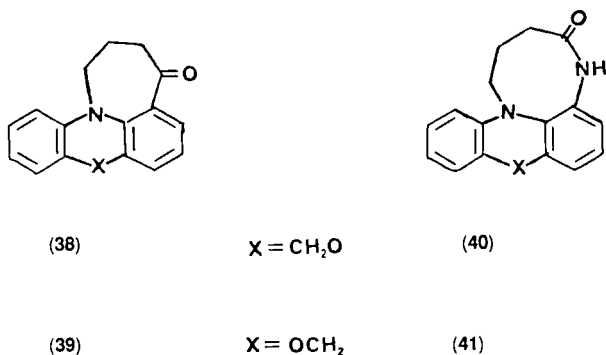


R = H, Ts

(36)

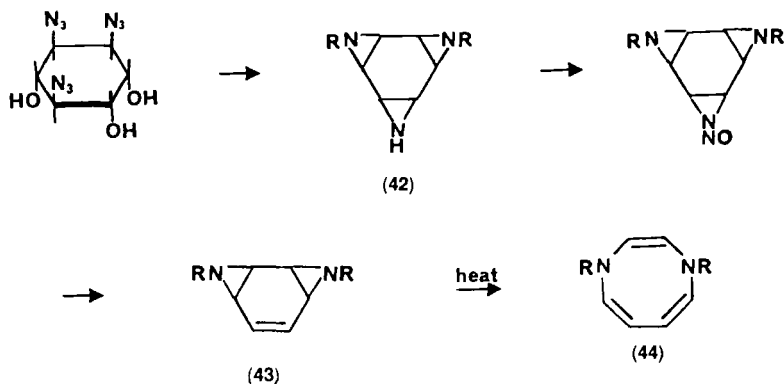


(37)

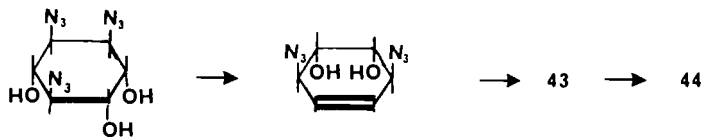


2. Ring Opening of Three-Membered Rings (i.e., Azahomobenzenes)

Two groups have developed synthetic methods for interesting 10 π -electron 1,4-dihydro-1,4-diazocines (see Section III). Prinzbach *et al.* mononitrosated *cis*-benzenetriamines **42**, then eliminated nitrous oxide to form *cis*-benzenediimines **43**. These latter compounds, upon warming, afforded the 1,4-diazocines **44** ($R = \text{Ts}$, CO_2Me , or Me) (Scheme 1) (75AG(E)348). Subsequent papers reported other derivatives of **44** ($R = \text{PhCH}_2$, CONMe_2 , NO , or Cl) (79AG(E)964; 80CB3161). An alternate route to these compounds (Scheme 2) was found to offer no advantage over the method shown in Scheme 1 (79AG(E)964). The parent compound **44** ($R = \text{H}$) could not be made by this method, but was prepared by reaction of urethane **44** ($R = \text{CO}_2\text{Me}$) with sodium methoxide. The parent compound could also be synthesized via the dianion **45** by reaction of **44** ($R = \text{CO}_2\text{Me}$, Ts , or CONMe_2) with potassium *t*-butoxide (79AG(E)964). Vogel and co-workers,

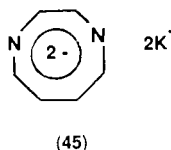


SCHEME 1



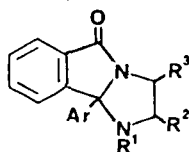
SCHEME 2

using a method similar to that shown in Scheme 1, prepared **43** ($R = \text{Mes}$), which ring-opened in refluxing acetone to **44** ($R = \text{Mes}$). Treatment of this latter compound with potassium amide afforded **45**. This salt could be converted into the parent **44** ($R = \text{H}$) plus various derivatives **44** ($R = \text{SiMe}_3$, Me , or CO_2Me) (79AG(E)962). (For a discussion of the structure and chemistry of these compounds, see Section III.)

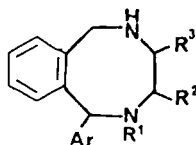


3. Ring Opening of Diazabicyclo[3.3.0]octanes (e.g., Imidazoisindolones and Pyrroloimidazoles)

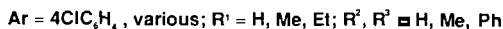
Access to the pharmacologically useful hexahydro-2,5-diazocines (see Section V) has been provided by reductive ring opening of imidazoisindolones. Sulkowski and co-workers, in most of such reports, reacted *o*-aroylbenzoic acids with 1,2-diamines, producing compounds **46**. These latter compounds were reduced with lithium aluminum hydride, affording diazocines **47**



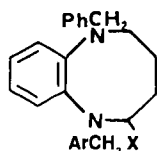
(46)



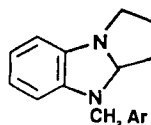
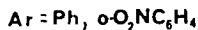
(47)



(67BRP1093064; 67FRP1487344; 67JOC2180; 67JOC3270; 67NEP6614399; 69JOC1720; 72USP3663532; 76USP3994920). The isomeric 1,6-benzodiazocine derivatives **48** were prepared by Grantham and Meth-Cohn. The



(48)

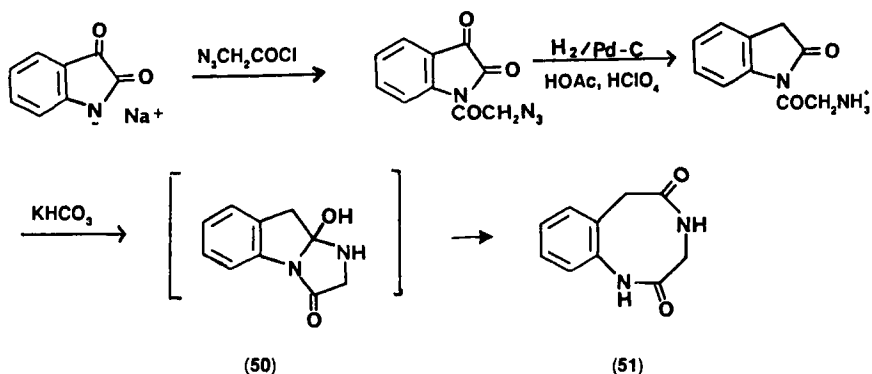


(49)

pyrrolidinobenzimidazoles **49** were quaternized at the bridgehead nitrogen with benzyl- or *o*-nitrobenzyl chloride. The resulting salts were treated with hydride, cyanide, and hydroxide nucleophiles to yield 1,6-benzodiazocines **48** (X = H), **48** (X = CN), and **48** (X = OH), respectively. The last compound was isolated along with an equimolar amount of its open-chain diaminoaldehyde tautomer (71JCS(C)1354). Muchowski synthesized bis-lactam **51** from sodioisatin according to Scheme 3. Although the imidazoisindolol **50** was not isolated, the final step most likely involved ring opening of a transient **50** (70CJC1946). (For a discussion of the chemistry of these compounds, see Section IV,B.)

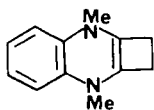
4. Ring Opening of Diazabicyclo[4.2.0]octanes

Shue and Fowler thermolyzed cyclobutene **52** and obtained **53** (R = Me) (71TL2437). (For a discussion of the chemistry and spectroscopy of **53**, a 14π -electron heterocycle, see Sections IV,A and III, respectively.) Lown *et al.* succeeded in isolating small quantities of diazocine **54** on photolysis of azetidinopyridine **55**. A compound such as **54** was postulated as an inter-

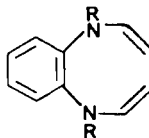


SCHEME 3

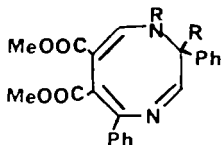
mediate in the reaction of 1,2-dialkyl-2,5-diphenyl-1,2-dihydropyrazines with dimethyl acetylenedicarboxylate (DMAD) to give azetidinopyridines **55** ($R = \text{alkyl}$) (75JOC3363). (For a discussion of the intermediacy of diazocines in the reactions of 1,2-dihydropyrazines with DMAD, see Section IV,D.) McOmie and co-workers oxidized diazabenzobiphenylene **56** with peracetic acid and obtained bislactam **57**, along with *o*-nitroaniline (78T495).



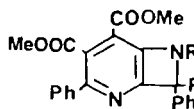
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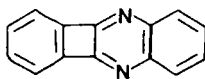
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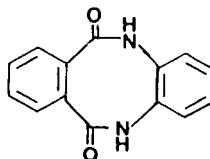
(54)



(55)



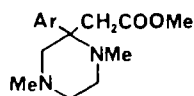
(56)



(57)

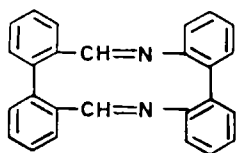
Sarges and Tretter found that the ester derivative of **16**, upon saponification and cyclodehydration, afforded diazocine **17** (see Section II,A,2). They also found that the ester of **16** underwent base-catalyzed Michael addition to give piperazine derivative **58**. Saponification of **58**, followed by treatment with DCC, yielded the ring-expanded diazocine **17** (74JOC1710).

An interesting ring-contraction route to a 1,4-diazocine was reported by Koch and Dessy, who electrochemically reduced the 12-membered cyclic diaza compound **59** and obtained a phenanthrodibenzodiazocine **60** as a minor product (the major product being an azepinodiazepine) (82JOC4452).

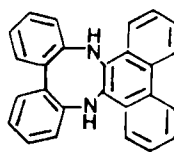


Ar = Ph, 2-Na

(58)



(59)

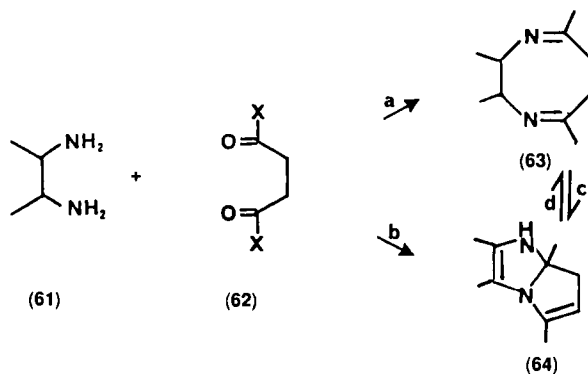


(60)

C. VIA CONDENSATIONS

1. Condensations between Dicarboxylic Acid Derivatives and 1,2-Diamines

Many early reports of condensations between 1,4-dicarbonyl compounds (**61**) and 1,2-diamines (**62**) to give 1,4-diazocines (**63**) must be considered suspect, since it has been subsequently demonstrated that in many cases the pyrroloimidazole system (**64**) is formed either directly (path b) or indirectly (paths a and c) (Scheme 4). [In fact, routes b and d have been used as an entry into the 1,4-diazocines by Sulkowski and co-workers and other groups

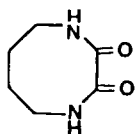


SCHEME 4

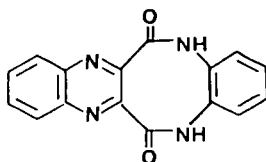
(see Section II,B,3.)] For a more detailed discussion of this problem, see Section II,C,3,b.

Lippert and Reid reported that heating a methanolic solution of dialkyl succinate and ethylenediamine (ED) produced bislactam **18** (39USP2156300). The same compound was prepared more recently using sodium isopropoxide as a catalyst. The isomeric 1,4-diazocine **65** was prepared by condensing oxalyl chloride with tetramethylenediamine (68MI1).

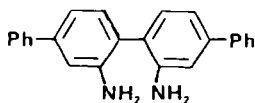
Fused-ring analogs of **18** and **65** have stimulated more interest than the parent molecule. Chattaway and Humphrey heated sodium dihydroxytartrate with *o*-phenylenediamine (OPD) and obtained a product to which they assigned structure **66** (29JCS645). The 1,4-diazocines that are bridged biphenyls have been of stereochemical interest (see Section III). Simpson *et al.* condensed quaterphenyl **67** with oxalyl chloride and produced bislactam **68**. However, an attempt to synthesize the diamine by lithium aluminum hydride reduction of **68** was unsuccessful (73JOC4428).



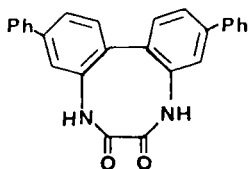
(65)



(66)



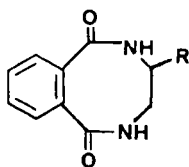
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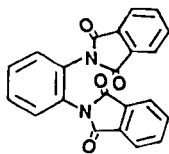
(68)

Stetter *et al.* reacted phthaloyl chloride with ED and OPD and reported the products as diazocines **69** (R = H) and **57**, respectively (58CB1775). However, Paudler and Zeiler have disputed these and earlier reports of 1,4-diazocine formation by reaction of 1,2-diamines with phthalic acid derivatives, and claim that the compound reported (58CB1775) as **57** is really bispthalimide **70**, and have themselves prepared authentic **57** by the reaction of OPD with diethyl phthalate in the presence of sodium hydride (69JOC2138). Wolfe and Hasan repeated the synthesis of **69** (R = H) by

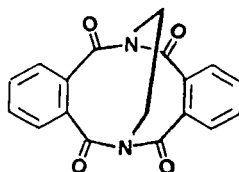
Stetter *et al.* (58CB1775), but failed to obtain the previously reported product, obtaining instead a compound they formulated as the diazecine derivative **71** (70CJC3566). Aubagnac *et al.* also prepared **72** ($R = H$) by the method of Paudler and Zeiler (69JOC2138), but attempts to convert it into the 10π -electron-conjugated system **53** ($R = H$) failed, ring contraction occurring instead (72BSF2868). Elguero *et al.*, as part of an NMR study of the stereochemistry of diazocines (see Section III), prepared **72** ($R = H, Me$) by reacting OPD with diethyl succinate and its 2-methyl derivative. Derivatives of **57** were prepared in a similar manner and converted into bis-(dialkylamino) derivatives **73** (85H1425) (see Section II,C,3b and IV,B). Reaction of diethyl pyridazine-4,5-dicarboxylate and its 3,5-dimethyl derivative with OPD in the presence of sodium hydride afforded diazocines **74**, the latter compound undergoing various ring contractions (see Section IV,C) (74JCS(P1)1022).



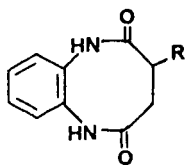
(69)



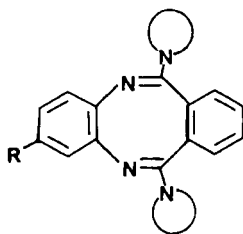
(70)



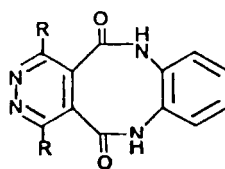
(71)



(72)

 $R = H, Me, NO_2$

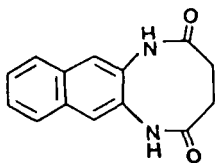
(73)

 $R = H, Me$

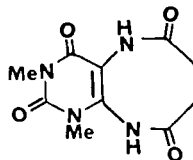
(74)

N,N'-Ditosyl-2,3-naphthalenediamine was reacted with succinoyl chloride in the presence of sodium carbonate to yield the naphthodiazocine **75** (84MI1). Thompson reacted 5,6-diamino-1,3-dimethyluracil hydrate with succinic and phthalic anhydrides and obtained **76** and **77**, respectively. When succinic anhydride was reacted with 2,3-diaminopyridine, however, only one amino group reacted to give an intermediate diamino acid, which cyclized to **22** (see Section II,A,2) (86JHC1545). Siemion and Wieland condensed homoanthranilic acid derivative **78** with 1-proline *p*-nitrophenyl ester and

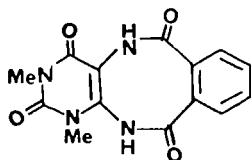
obtained diazocine **79**, a cyclic peptide like molecule that was the object of stereochemical study (see Section III) (77T155).



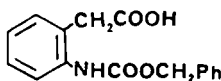
(75)



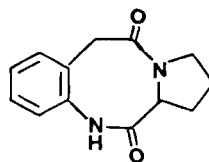
(76)



(77)



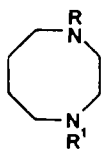
(78)



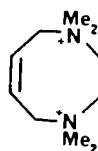
(79)

2. Condensations of Diamines with Saturated Electrophilic Carbon

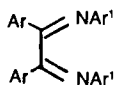
The completely saturated unsubstituted molecule, octahydro-1,4-diazocine (**80**, $R = R' = H$) has been prepared by condensing tetramethylene bromide with *N,N'*-ditosyl-ED in refluxing alcoholic potassium hydroxide (74MI1). The unsubstituted and *N,N'*-dialkylated compounds **80** ($R = PhCH_2$, $R' = i-Pr$ and $PhCH_2$; $R = H$, $R' = i-Pr$) have been made by reacting tetramethylene bromide with appropriately substituted derivatives of ED (75MI2). The unsaturated diammonium salt **81** has been prepared by reaction of *cis*-1,4-dihalo-2-butene with *N,N,N',N'*-tetramethyl-ED (73MI1; 75MI1). Singh and Mehrotra reported a novel method of synthesis of substituted diazocines. Dianils **82**, prepared from Schiff bases $ArCH=NAr^1$, were reductively converted into sodium salts, then heated with 1,4-dichlorobutane to afford diazocines **83** (81H1341).



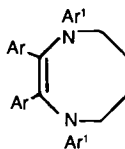
(80)



(81)

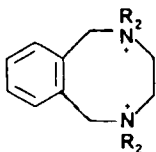


(82)

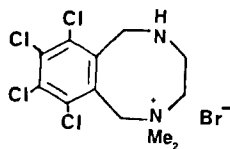


(83)

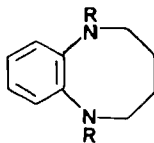
There are numerous examples of syntheses of fused-ring 1,4-diazocines. In some early work, Scholtz prepared the bisammonium salt **84** [$R_2 = (CH_2)_4$] by reacting *o*-xylylene dibromide with 1,2-dipiperidylethane (02CB3047). Noguchi and Uchida condensed *o*-xylylene dibromide with *N,N,N',N'*-tetramethyl-ED and isolated the bis salt **84** ($R = Me$) (75MI2). Rosen *et al.* reacted 3,4,5,6-tetrachloro-*o*-xylylene dibromide with *N,N'*-dimethyl-ED and obtained salt **85** (58JA935). Stetter treated bissulfonamides of OPD with 1,4-dibromobutane and isolated benzodiazocines **86**. These compounds could be hydrolyzed to either monosulfonamides or free diamine, depending on acid concentration and condition (53CB197; 72BSF2868). Stetter condensed the bistosyl derivative of 2,2'-diaminobiphenyl with 1,2-dibromoethane in the presence of sodium *tert*-butoxide and obtained the bridged biphenyl **87** (53CB380). Schroth and Streckenbach prepared the



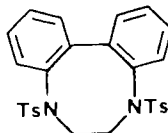
(84)



(85)



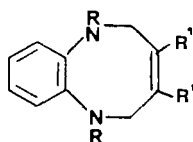
(86)



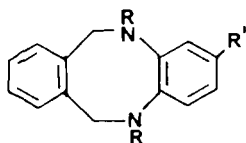
(87)

N,N'-dimethyldiazocine **88** ($R = Me$, $R^1 = H$) by two different methods. The first method involved reacting *N,N'*-dimethyl-OPD with *cis*-1,4-dichloro-2-butene. The second procedure used the method of Stetter (53CB197) to synthesize **88** ($R = R^1 = H$); this compound was methylated

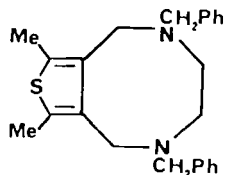
to give **88** ($R = \text{Me}$, $R^1 = \text{H}$). Also, OPD bissulfonamide was reacted with *cis*-1,4-dibromo-2,3-dimethyl-2-butene to give a bissulfonamide, which, when detosylated, afforded **88** ($R = \text{H}$, $R^1 = \text{Me}$). *N,N'*-Dimethyl-OPD and *o*-xylylene dibromide gave the dibenzo[*b,f*]-1,4-diazocine **89** ($R = \text{Me}$, $R^1 = \text{H}$) (63ZC465). Three groups reported that **89** ($R = \text{Ts}$, $R^1 = \text{H}$) resulted from reaction of *N,N'*-bistosyl-OPD with *o*-xylylene dibromide (63ZC465; 65JOC43; 69JCS(C)882). This bissulfonamide was detosylated to afford free amine **89** ($R = R^1 = \text{H}$) (63ZC465; 69JCS(C)882). In an expansion of this work, numerous ring-substituted derivatives of *N,N'*-OPD bistosylate and *o*-xylylene dibromide yielded substituted compounds **89** ($R = \text{Ts}$, $R^1 = \text{various}$). These compounds were partially and fully detosylated (70JCS(C)1161). Thiophenodiazocine **90** was synthesized from *N,N'*-dibenzyl-ED and 3,4-bis(chloromethyl)-2,5-dimethylthiophene (64IZV2182). Yale and Spitzmiller heated *N,N'*-(*o*-phenylene) bisformamide with *o*-xylylene dibromide in the presence of potassium carbonate in dimethylformamide (DMF) and obtained the diazocine **89** ($R = \text{CHO}$, $R^1 = \text{H}$) (74GEP2334783; 76JHC443).



(88)



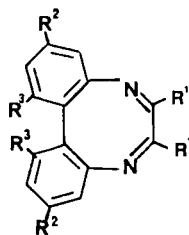
(89)



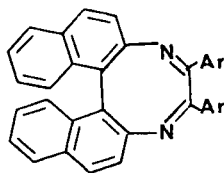
(90)

3. Condensations of Diamines with Aldehydes and Ketones

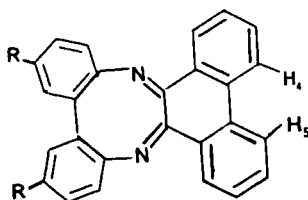
a. *Synthesis of Biaryl Derivatives.* These compounds, called dibenzo[*e,g*]-1,4-diazocines, have been known for almost a century and are synthesized by reacting 2,2'-diaminobiaryls with α -diketones. Compounds prepared were **91** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) (1892CB3287; 1893CB1703; 59JOC306; 71JCS(C)1712; 73JCS(P2)973); **91** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$) (01CB3330); **91** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{F}$) (55JA2272); **91** ($R^1 = \text{Ph}$, $R^2 = \text{CO}_2\text{H}$, $R^3 = \text{H}$) (52JCS1527; 64JCS2326); **91** ($R^1 = \text{Ph}$, $R^2 = \text{CO}_2\text{Me}$, $R^3 = \text{H}$) (63JOC4290; 71JCS(C)1712); **91** ($R^1 = p\text{-tol}$, $R^2 = R^3 = \text{H}$) (52JCS5047); **91** ($R^1 = R^3 = \text{Me}$, $R^2 = \text{H}$) (84JCS(P1)2013); **91** ($R^1 = 2\text{-pyr}$, $R^2 = \text{H}$, $R^3 = \text{Me}$) (85TL2077); **92** ($\text{Ar} = 2\text{-pyr}$) (85TL2077); **92** ($\text{Ar} = \text{Ph}$, $\text{O}_2\text{NC}_6\text{H}_4$) (29LA183); **93** ($R = \text{H}$) (29JCS733; 73JCS(P2)973; 82JOC4452); **93** ($R = \text{Br}$) (29JCS733). Some of these were also prepared in optically active form for stereochemical studies (see Section III).



(91)



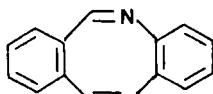
(92)



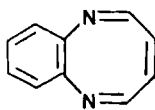
(93)

b. *The Controversial History of Dibenzo[b,f]-1,4-diazocines.*

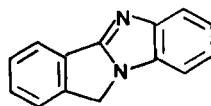
Although saturated analogs of 1,4-diazocine have been prepared (see Section II.C.2), the completely conjugated unsubstituted di-Schiff base (**5,6**) and fused-ring analogs, such as **94** and **95**, have eluded isolation, despite a long history of attempted syntheses, especially attempts to make **94** and **95**.



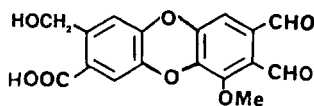
(94)



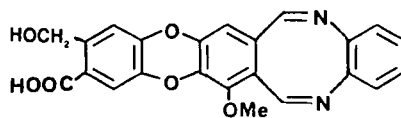
(95)



(96)



(97)

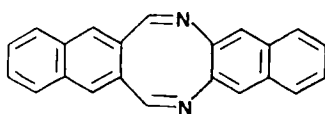


(98)

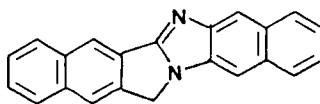
The first reported condensation of *o*-phthalaldehyde with OPD was that of Thiele and Falk, who obtained a solid claimed to be isoindolobenzimidazole **96**, not diazocine **94** (06LA114). This assignment was later confirmed by chemical evidence (18LA1; 35JCS1796), although Betrabet and Chakravarti disputed the product assignment, claiming that diazocine **94**

was the product (30JIC191). About the same time, Kondo and Tomita reacted the dibenzodioxin **97** with OPD and claimed to have isolated a "monoazine" of structure **98**, although no supporting evidence was offered (32LA104). More recently, Ried and co-workers condensed OPD with 2,3-naphthalenedicarboxaldehyde, 2,3-naphthalenediamine with *o*-phthalaldehyde, and 1,2- and 2,3-naphthalenediamine with 2,3-naphthalenedicarboxaldehyde and reported the products' structures as diazocines (e.g., **99** was assigned as the structure of the product of the last reaction) (56CB708; 59CB2902). Several years later, Sparatore and Bignardi again confirmed Thiele and Falk's assignment of **96** to the structure of the product of condensation of OPD and *o*-phthalaldehyde (06LA114), and also postulated a similar structure (i.e., an azepinobenzimidazole) for the product of condensation of OPD with 2,2'-biphenyldicarboxaldehyde, as well as related condensations (62G606).

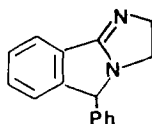
Final unequivocal spectroscopic evidence against the 1,4-diazocine structure, and in favor of the isoindolobenzimidazole structure, for the aromatic 1,2-dicarboxaldehyde-aromatic 1,2-diamine condensations was presented by Amos and Gillis (64AJC1440) and by Perlmutter and Knapp (67JOC2350). The former workers confirmed Thiele and Falk's assignment (06LA114), whereas the latter extended the same assignment to the naphtho-fused compounds of Ried and co-workers (56CB708; 59CB2902). For example, structure **99** was reassigned structure **100**. At about this time, Sternbach and co-workers extended the aforementioned condensations to that of ED with *o*-benzoylbenzaldehyde, and obtained the isoindoloimidazole **101**, not a diazocine (68JOC2874). Bindra and Elix, in a mechanistic study of the 2,2'-biphenyldicarboxaldehyde-OPD condensation (62G606), demonstrated that the azepinobenzimidazole **102** arose via an intermolecular hydride shift,



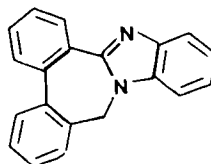
(99)



(100)



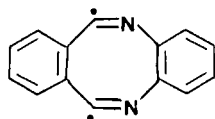
(101)



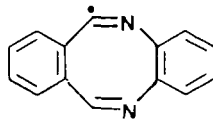
(102)

and suggested that a similar mechanism may be operating in the formation of **96** and **101** (69T3789).

Interestingly, Sarkisian and Binkley photolyzed the benzocyclobutaquinoxaline **56** in methanol and obtained isoindolobenzimidazole **96**. They postulated the diazocine diradical **103** and monoradical **104** as photolysis intermediates (70JOC1228). [Peracid oxidation of **56** did afford the diazocinedione **57** (see Section II,B,4) (78T495).] During this period, Reid and

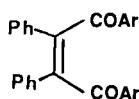


(103)

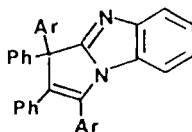


(104)

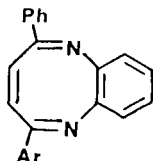
Lantzsch reacted OPD with diaroylstilbenes **105** and obtained pyrrolobenzimidazoles **106**, not diazocines (71LA97). Shevchuk *et al.*, however, condensed 1-benzoyl-2-aroylethylenes with OPD and claimed to have formed 1,6-benzodiazocines **107** on the basis of limited spectroscopic evidence (70JOU1110). These results were disputed by three groups. Bindra and LeGoff claimed the compound reported (70JOU1110) as **107** (Ar = Ph) was really dihydrobenzodiazocine **53** (R = Ph) (74TL1523). However, Perlmutter and Trattner (74JHC89, 74JHC847), and later Bass *et al.* (75TL2073), gave unequivocal spectroscopic evidence that the compound was not a diazocine, but pyrrole **108**. Hiremath *et al.* condensed indole-2,3-dicarboxaldehydes



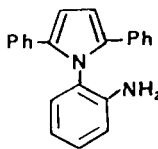
(105)



(106)

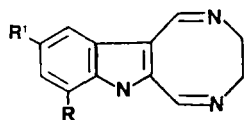


(107)

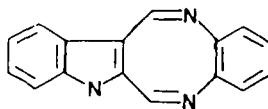


(108)

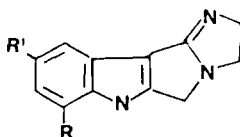
with ED and OPD and reported the products as indolodiazocines **109** and benzoindolodiazocines **110**, respectively (79IJC(B)130). However, the weight



(109)



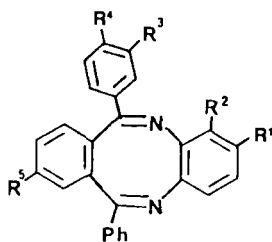
(110)



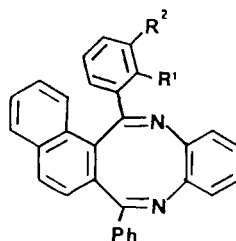
(111)

of previous experience with these condensations (*vide supra*) leads one to favor a benzimidazole structure such as **111** for the condensation products.

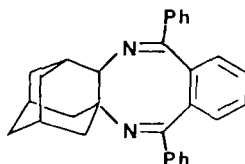
The first completely conjugated $[b,f]$ 1,4-diazocine (**112**, $R^1-R^5 = H$) was synthesized by Perlmutter from OPD and *o*-dibenzoylbenzene, using aluminum chloride as catalyst (68CC1202). Improved yields of the parent **112** and substituted derivatives were realized by Ollié and Solladié (75S246). Solladié and co-workers prepared and resolved dissymmetric derivatives of **112** ($R^1-R^5 = H, Me$; and $R^1 = R^2 = R^4 = R^5 = H, R^3 = CHO$) and **113** as part of stereochemical studies of these compounds (78JCR(S)408) (see Section III).



(112)



(113)

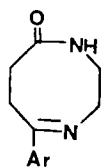


(114)

An adamantane-fused 1,4-diazocine **114** was formed by reacting 1,2-diaminoadamantane with *o*-dibenzoylbenzene (87UP1). The diazocinedione **57** and substituted **57** were converted into the bisamidines **73** by reaction with secondary amines in the presence of titanium tetrachloride/anisole complex (85H1425). (See Section II,C,1 and IV,B).

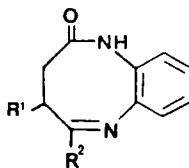
4. "Mixed" and Other Condensations

A series of medicinally useful diazocines, benzodiazocines, and dibenzodiazocines was prepared by Sulkowski and co-workers (see Section V). The diazocinones **115** were prepared by reacting 3-acyl- or 3-aroilpropionic acids with ED. The benzo-1,6-diazocinones **116** were made by condensing these keto acids with OPD (66USP3293243). The benzo- and pyridino-2,5-diazocinones **117** and **118** were prepared by condensing the appropriate 1,2-diamines with 2-aroilbenzoic acids and 3-(*p*-chlorobenzoyl)picolinic acid, respectively. If OPD was utilized instead of 1,2-alkylenediamines, a di-benzo-1,4-diazocine related to (**10**) and pyridinobenzo-1,4-diazocine (**119**), respectively, were obtained. By condensing ED with 2-benzoylcyclohexanecarboxylic acid and 2-benzoylcyclohexenecarboxylic acid, **120** and **121**, re-



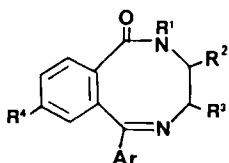
Ar = 4OMeC₆H₄,
4ClC₆H₄,
2-thienyl

(115)



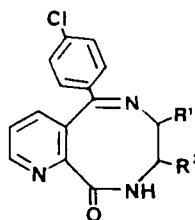
R' = H, Me
R'' = Me, Ph

(116)



R' = H, Me, Et
R'' = R''' = H, Me, OH
R'' = H, NO₂
Ar = various

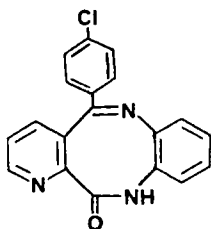
(117)



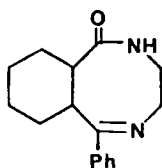
R' = R'' = H, Me, OH

(118)

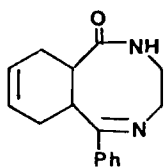
spectively, were also synthesized. [A number of benzodiazocinones were reduced to the corresponding hexahydro derivatives (64BEP646221).] Useful diazocinones **122** (see Section V) were prepared from methyl 3-formylpropionates with N-monosubstituted ED derivatives (80MIP1; 81JAP81-154468).



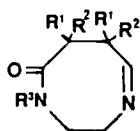
(119)



(120)



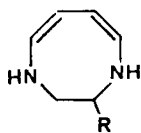
(121)



$R^1 = R^2 = H$
 $R^3 = \text{long chain of type}$
 $-R^1-O-R^2-O-R^3-N-R^1-N-$

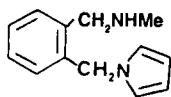
(122)

In a novel 1,4-diazocine synthesis, diacetylene was condensed with ED and 1,2-propylenediamine to afford diazocines **123** (63DOK1353). Nakamura and Kamila ran a Mannich condensation with benzoylpyrrole **124** and

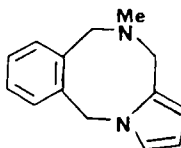


$R = H, Me$

(123)

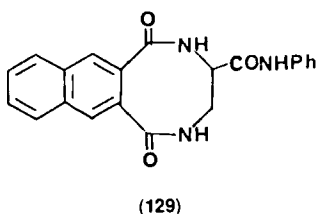
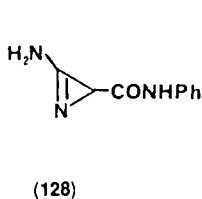
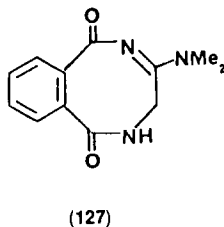
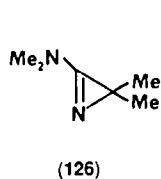


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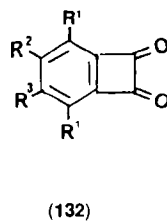
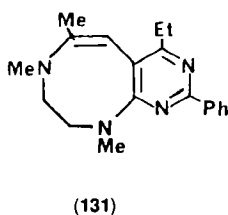
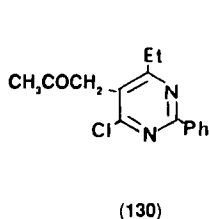


(125)

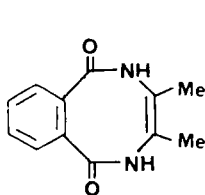
formaldehyde and obtained the benzopyrrolodiazocine **125** (74CPB2142). Another novel reaction was reported by Schmid and co-workers, who condensed azirine **126** with phthalimide to yield diazocine **127** (77HCA2476). Similarly, Ereemeev *et al.* treated azirine **128** with phthalic and 2,3-naphthalic anhydrides and obtained **69** and **129**, respectively (85KGS848).



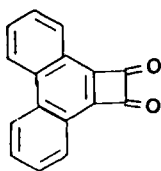
Wolfers *et al.* reported that acetonylechloropyrimidine **130** reacted with *N,N'*-dimethyl-ED, affording the pyrimidinodiazocine **131**. However, **130** condensed with primary diamines to yield pyrrolopyrimidines (75H187). In a series of papers, McOmie and co-workers investigated the reactions of benzocyclobutene-1,2-diones **132**. Reaction of unsubstituted **132** with OPD and ring-substituted OPD derivatives gave unsubstituted and substituted benzodiazabenzobiphenylenes **56**. [Peracetic acid oxidation of unsubstituted **56** afforded the 1,4-diazocine **57** (see Section II,B,4) (78T495).] When **132** ($R^1 = R^2 = R^3 = H$) was heated with aliphatic and heterocyclic 1,2-diamines, diazabiphenylenes were *not* obtained. However, one diamine, diaminomaleonitrile, did condense with **132** to form benzo-2,5-diazocine **133** (79T241). When substituted diones **132** were reacted with OPD, the type of product formed varied with the nature of the substitution in **132**. The



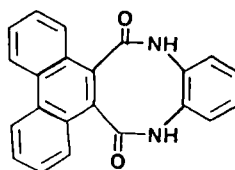
4-methoxy, 4,5-dimethoxy, and 4,5-dibromo derivatives of **132** afforded substituted **57**. Reaction of OPD with α -diketone **134** yielded phenanthrobenzodiazocine **135** (81JCS(P1)988). In related work, Toda and co-workers found that when dione **136** was condensed with OPD in carbon tetrachloride at room temperature, a cyclobutaquinoxaline was obtained, but in the presence of a radical initiator, bromotrichloromethane, the diazocine **137** was formed (83BCJ3193).



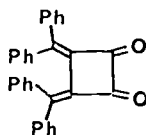
(133)



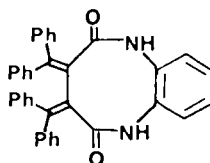
(134)



(135)



(136)

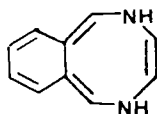


(137)

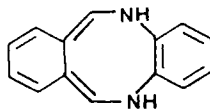
III. Theoretical and Structural Studies

Hückel calculation on the 8π -electron 1,4-diazocine (**5**) gave a resonance energy twice as great as those for the 1,3- and 1,5-isomers (75T295). In a quantum-mechanical study of a number of 10π -electron oxa and aza analogs of cyclooctatetraene and its benzo derivatives, Ponce and co-workers found that the 1,4-diazocines **44** ($R = H$), **53** ($R = H$), **138**, and **139** are not as aromatic as the 1,2-diazocines, the former compounds having a fair amount of bond alternation (75MI3). Molecular-orbital calculations on compound **5**, using the PPP method, failed to produce a solution corresponding to a C_{2v} π -delocalized structure (in contrast to results for the isomeric 1,3-diazocine). It was concluded that the 1,4-diazocine (**5**) has about the same antiaromatic character as cyclooctatetraene itself, and more than the 1,3- (or 1,5-) diaza isomers (83MI1). Shue and Fowler prepared the 14π -electron heterocycle **53** ($R = H$) (see Sections II,B,4 and IV,A) and concluded from comparison of its pK_a and proton NMR chemical shifts with typical enamines that **53** ($R = H$)

was nonaromatic, although the small differences in vinylic coupling constants compared to those of 1,3-cyclohexadiene did suggest the presence of considerable delocalization in the eight-membered ring (71TL2437).



(138)



(139)

Michl and co-workers calculated magnetic circular dichroism (MCD) spectra for the 10π -electron 1,4-diazocine **44** ($R = H$) as well as the isomeric 1,2-diazocine. Compound **44** ($R = H$) was calculated to be definitely a single-soft chromophore. MCD provides a measure of the difference between absorption of left- and right-handed circularly polarized light propagating along the direction of the magnetic field. MCD spectra distinguish between two types of chromophores: "hard" (MCD spectra unaffected by heteroatoms or substituents), and "soft" (MCD spectra sensitive to heteroatoms and $\pm I$, $\pm E$ substituents). In contrast to the 1,2-diazocine **140**, the 1,4-diazocine **44** ($R = H$) is calculated to be a soft chromophore, similar to the carbocyclic $4n + 2$ annulenes such as cyclooctatetraene dianion (**141**). The calculated spectrum was verified by the actual spectra of **44** and derivatives ($R = SiMe_3$, Me, CO_2Me). The various substituents affect the chromophore as predicted, including **44** ($R = CO_2Me$), which is predicted to be nonplanar (and verified by X-ray diffraction) (77MI1; 81JOC3306).

In a series of papers on the synthesis (see Section II,B,2) and properties of the 10π -electron 1,4-diazocine **44**, **142**, its dianion (**45**, **143**), and its N,N' -disubstituted derivatives, groups headed by Prinzbach (75AG(E)348; 79AG(E)964; 80CB3161) and Vogel (79AG(E)962) carried out spectroscopic and X-ray crystallographic studies, the results of which are outlined below.

1. All compounds to type **142** showed little difference in H_A , H_B , and H_C compared with analogously substituted triazonines (75AG(E)348).

2. The ^{13}C - and 1H -NMR spectra of compounds **142** ($R = H$) (79AG(E)962; 79AG(E)964; 80CB3161); **142** ($R = Me$, CO_2Me) (75AG(E)348; 79AG(E)962; 79AG(E)964; 80CB3161); **142** ($R = Ts$) (75AG(E)348; 79AG(E)962; 80CB3161); **142** ($R = CONMe_2$, $PhCH_2$) (79AG(E)962, 80CB3161); **142** ($R = SiMe_3$, MeS) (79AG(E)962; and **143** (79AG(E)962, 79AG(E)964), when compared with the spectra of triazonines and pyrroles, demonstrated diamagnetic ^{13}C shifts and paramagnetic N-substituted proton shifts for **142** ($R = H$) (79AG(E)962; 79AG(E)964; 80CB3161).

3. The chemical shift differences between H_A and H_B in **142** ($R = Me$) are

less than those for the corresponding protons in benzodiazocine **53** ($R = H$) (71TL2437).

4. The UV spectrum of **142** ($R = H$) was similar to that of the cyclooctatetraene dianion (**141**) (79AG(E)962, 79AG(E)964).

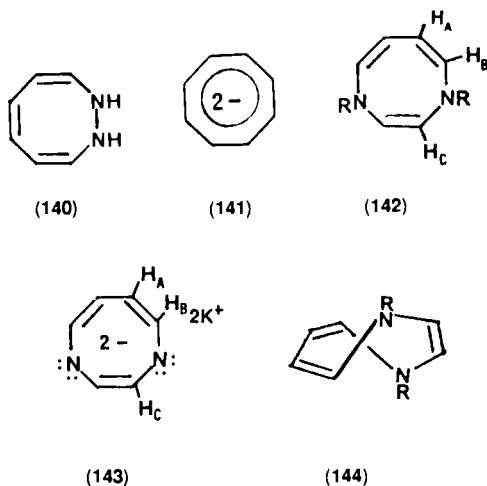
5. For **142** ($R = H$), no valence bond tautomers were detected at equilibrium, thus leading to a possible stabilization energy of 20 kcal/mol for **142** ($R = Me$) (79AG(E)964).

6. Compound **142** ($R = Me$) formed a stable charge transfer complex with 1,3,5-trinitrobenzene (79AG(E)964).

7. Compounds **142** ($R = PhCH_2$, CO_2Me) reacted readily with dienophiles to form Diels–Alder adducts (79AG(E)964; 80CB3161).

8. The precursors *cis*-diazabis(σ -homobenzenes) **43** underwent a cycloreversion to diazocines (**44**, **142**) at varying rates depending on the N-substituent, but all proceed more rapidly than *cis*-benzene dioxide (80CB3161).

These results allow division of the diazocines into two types: (1) planar, diatopic, "aromatic" (**142**, $R = H$, Me, $CONMe_2$, $SiMe_3$) and (2) nonplanar, nondiatopic, nonaromatic, having a twist conformation (**144**, $R = Ts$, $PhCH_2$, Mes, CO_2Me).

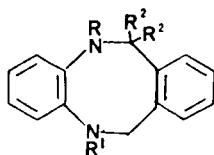


All of the above findings were corroborated by X-ray crystallographic structures of **142** ($R = H$) (79AG(E)962, 79AG(E)964), **142** ($R = CO_2Me$, $CONMe_2$) (79AG(E)964), and **142** ($R = Mes$, $SiMe_3$) (79AG(E)962). The subtlety of the two opposing forces (toward nonaromatic nonplanarity and aromatic planarity) is illustrated for **142** ($R = CONMe_2$). The NMe_2 group causes a steric inhibition of NCON resonance (which would prevent $4n + 2\pi$ delocalization), which in concert with steric inhibition of coplanarity makes

even this bulky *N,N*-dimethylamide planar and diatopic, in contrast with compounds **142** ($R = \text{CO}_2\text{Me}$, Ts, Mes) (79AG(E)964). Interestingly, it was pointed out (79AG(E)964) that the aromaticity of **142** ($R = \text{H}$) was at odds with the theoretical findings of Ponce and co-workers (75MI3).

The semiempirical all-valence electron CNDO/2 and INDO methods were used to calculate the total energy, binding energy, ionization potential, and dipole moment of diazocine **18** and higher ring homologs (76ZN1677). Also calculated were the transannular C—N interatomic distance and C—N orbital atomic population (78T53).

Draney and Kingsbury found that the free radical di-*tert*-butyl nitroxide caused significant concentration-dependent ^{13}C -chemical shift changes in diazocine **80** ($R = R^1 = \text{H}$) and many other molecules, especially those with heteroatoms. The shifts, depending in a roughly statistical manner on x of CH_x , were interpreted in terms of association equilibria (81JA1041). The photoelectron spectra of benzodiazocine **86** ($R = \text{Me}$) and other homologous and acyclic OPD derivatives were reported, but did not appear to be useful to determine conformations because of the strong interaction between the effects of bending and twisting at nitrogen on ionization potentials (81JOC283). An investigation of the mass spectral behavior of dibenzocine **145** ($R = \text{H}$, Me; $R^1 = \text{H}$, Me, D; $R^2 = \text{H}$, D) was reported. One process that occurred resulted in the loss of a C_7H_7 radical (73OMS65).

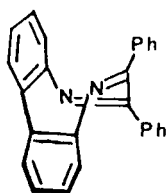


(145)

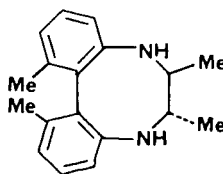
A linear relationship was found between the ^{13}C -chemical shift differences in the γ and β carbons of *N*-acylproline-containing peptides and the angle θ described by the proline carbonyl group and the β carbon. This relationship was used to determine the conformation of the diazocine **20** (see Section II,A,2), the angle θ being between 75 and 80° (75AG(E)702). This compound showed a strong positive Cotton effect centered around 235 nm . The aforementioned ^{13}C -NMR study demonstrated that the right-handed helix was the preferred conformation of this inherently dissymmetric chromophore, a result similar to that for twisted 1,3-dienes or α,β -unsaturated ketones, and opposite to that for twisted biphenyls (77T155).

A 1,4-diazocine whose stereochemistry has been frequently studied is dibenzo[*e,g*]-1,4-diazocine **91** and related molecules. These are optically stable compounds, and have been the subject of investigation both for the

relationship of their racemization to ring inversion and for their chiroptical properties. The dibenzodiazocine **91** ($R^1 = \text{Ph}$; $R^2 = \text{COOH}$; $R^3 = \text{H}$) (52JCS1527) had been resolved using solvent temperatures near 80°C , so that the compound was optically stable. [Subsequent X-ray diffraction studies on **91** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) confirmed its expected tub shape (**146**) (73JCS(P2)1929), a shape similar to that of cyclooctatetraene.] Also, optically active **92** ($\text{Ar} = \text{Ph}$) has been prepared (see Section II,C,3,a) (29LA183) and must have been stable to 200°C . Allinger *et al.* resolved **91** ($R^1 = \text{Ph}$, $R^2 = \text{COOH}$, $R^3 = \text{H}$) and when an attempt was made to measure the rate of racemization of the dimethyl ester by heating it above 250°C , it decomposed (see Section IV,C). The rate of this decomposition allowed an estimation of 48 kcal/mol as a lower limit for the ΔF^\ddagger of racemization (63JOC4290). At about this time, Hall and Insole could not racemize the optically active diazocine **91** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Me}$), but had more success with the compound without the *o,o'*-dimethyl substitution. They were able to measure the rate of loss of optical activity of **91** ($R^1 = R^3 = \text{H}$, $R^2 = \text{COOH}$), but did not isolate appreciable amounts of racemic dicarboxylic acid. Although the process measured was, like that of Allinger *et al.* (63JOC4290), a decomposition, the calculated ΔF^\ddagger of 44 kcal/mol was claimed as a lower limit for diazocine ring inversion (64JCS2326). [If one allows for steric hindrance resulting from the biphenyl system, the minimum E_{act} for diazacyclooctatetraene inversion is 20 kcal/mol less (63JOC4290).]



(146)



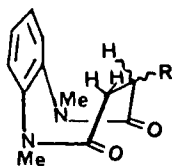
(147)

Insole has reviewed the assignment of absolute configuration of diazocines **91** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Me}$; $R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) and has reported ultraviolet (UV) and circular dichroism (CD) spectra of these compounds and of **91** ($R^1 = \text{Ph}$, $R^2 = \text{CO}_2\text{H}$, $R^3 = \text{H}$). The absolute configuration of this latter compound has been assigned (71JCS(C)1712).

The ^1H -NMR spectra of diazocines **91** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) and **93** ($R = \text{H}$) confirm twisted conformations of the eight-membered ring in these compounds. The twist in **93** is evidently so great that protons H_4 and H_5 , expected to be coplanar and therefore deshielded, do not resonate at the chemical shift expected of normal phenanthrene protons (73JCS(P2)2131). The conformation of diazocine **147** was determined by X-ray diffraction.

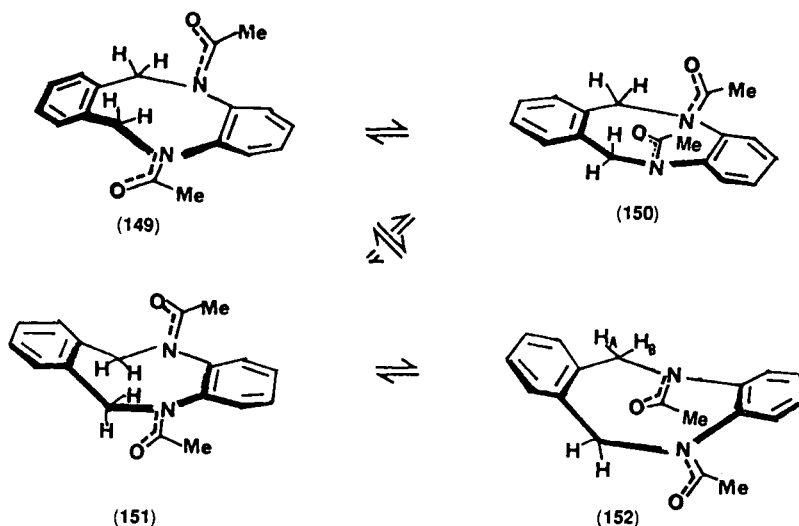
Analysis of spectra indicated a similar shape in solution. The CD spectrum of **147** was compared to those of differing torsion angle θ , and seemed invariant from 0 to 120°, but similar comparisons using the hydrochloride salt of **147** showed an inversion at a θ of about 90° (84JCS(P1)2013).

Addition of chiral, (*l* or *d*) nonmesomorphic dinaphthodiazocine **92** (Ar = Ph) to 1-menthol caused an optical rotation exceeding the value in isotropic solution by a factor of 10³ and a CD characteristic of cholesteric phases. These effects were ascribed to a nematic-cholesteric phase transformation, i.e., induction of helical superstructure in 1-menthol by **92** (Ar = Ph) (71N599). In very similar work, a solution of **92** (Ar = Ph) in nematic liquid crystals [such as a mixture of the isomeric N-oxides of *p*-methoxybenzilidene- and *N*-(*p*-ethoxybenzilidene)-*p*'-butylaniline] produce infrared rotary dispersion curves with anomalies having unexpectedly large amplitudes (72AG(E)227). Vögtle *et al.* reported that the optically active diazocines **91** (R¹ = α -pyr, R² = H, R³ = Me; and R¹ = 6-Me-2-pyr, R² = R³ = H) were highly Cu(I)-selective chiral ligands, their CD spectra being strongly cation dependent [i.e., different for other cations such as Zn(II), Ba(II), Mn(II)]. However, **91** (R¹ = 6-Me-2-pyr, R² = R³ = H) formed a much more stable complex than **91** (R¹ = α -pyr, R² = H, R³ = Me), the former compound forming a 2:1 ligand:Cu(I) complex (85TL2077).



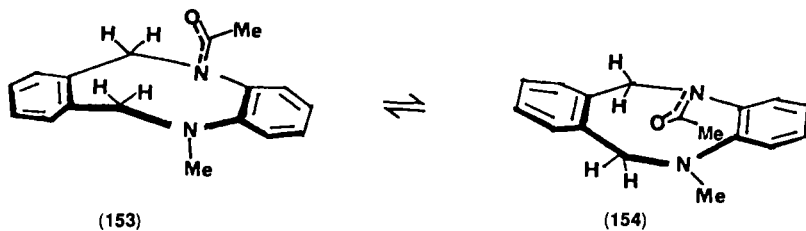
(148)

Another type of 1,4-diazocine of stereochemical interest is that bearing an *N,N'*-tetramethylene-*o*-phenylenediamine moiety, exemplified by structures **86** and **89**. A proton-NMR study showed that the heterocyclic ring of an *N,N'*-disubstituted benzo-1,6-diazocine is in boat conformation **148**, the boat \rightleftharpoons boat interconversion barrier being more than 25 kcal/mol (76CJC1135). Saunders and Sprake used UV and ¹H-NMR spectroscopy to study the *N,N'*-diacetyl-5,6,11,12-tetrahydridibenzo[*b,f*]-1,4-diazocine and concluded that there are four possible conformations (Scheme 5) with the interchange **150** \rightleftharpoons **151** (or **149** \rightleftharpoons **152**) occurring more readily than **149** \rightleftharpoons **150** (or **151** \rightleftharpoons **152**). In a similar manner, the conformations **153** \rightleftharpoons **154** were reported to be favored for the *N*-methyl-*N'*-acetyl derivative (Scheme 6) (72JCS(P2)1660).

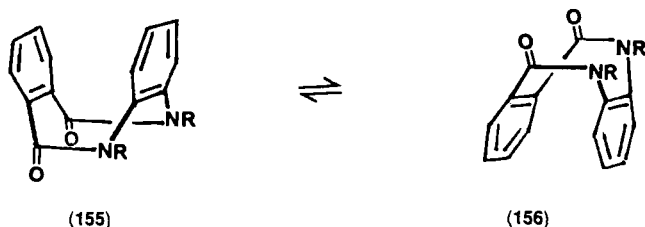


SCHEME 5

In contrast to the bislactone analogs, the bislactam **57** showed no ^1H -NMR spectrum change up to $+180^\circ\text{C}$, indicating a boat (**155**) \rightleftharpoons boat (**156**) interconversion barrier of greater than 27 kcal/mol (Scheme 7). This supported the view that the resonance stabilization of cis amide linkages is considerably greater than that of cis ester linkages (the isomeric 1,5-diazocine gave the same results) (73CC571; 74T1903). Ollis and co-workers also studied the temperature-dependent ^1H -NMR spectra of 1,4-diazocines **89** (along with the isomeric 1,5-diazocines, and thia analogs, as well as corresponding carbocycles). They concluded that the processes occurring involve interconversion between the three low-energy diastereomeric conformations (and their enantiomers): the chair (**157**), boat (**158**), and twist-boat (**159**). The boat \rightleftharpoons boat inversions were believed to proceed via a folded boat transition state, whereas chair \rightleftharpoons boat interconversions proceeded most probably via a transition state in which one benzene ring is

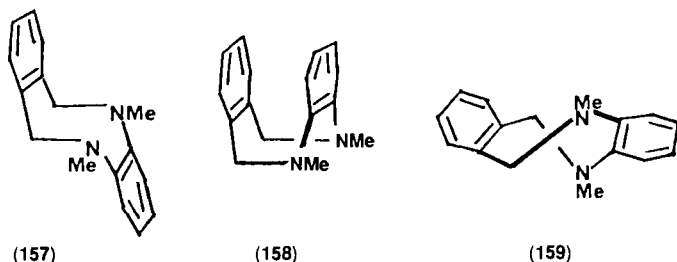


SCHEME 6



SCHEME 7

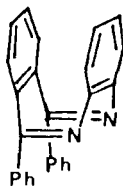
coplanar with six of the eight atoms of the central eight-membered ring (73JCS(P1)205). Interestingly, the *N,N'*-dibenzyl derivative **89** ($R = \text{PhCH}_2$, $R^1 = \text{H}$) showed no temperature dependence at temperatures well below those for other derivatives, possibly indicating a very rapid conformational



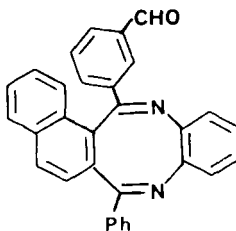
change. The conclusions from the above NMR line-shape analyses were corroborated using molecular mechanics calculations (74T1903). Sauriel-Lord and St.-Jacques have reported a dynamic NMR study similar to that of Ollis *et al.* (74T1903), in which they studied the temperature dependence of the ^1H -NMR spectra of **89** ($R = \text{Me}$, $R^1 = \text{H}$). Their findings for the diacetyl derivative were in accord with previous ones (74T1903), but they also found a new dynamic process, that of hindered amide rotation. The NMR study of the dimethyl derivative indicated a low-temperature spectral change that was best interpreted as a rapid boat–boat inversion similar to that of the carbocyclic analog. The dibenzyl derivative **89** ($R = \text{PhCH}_2$, $R^1 = \text{H}$) (for which Ollis and co-workers found no spectral change) (73JCS(P1)205) most likely undergoes a rapid tub–tub inversion (75CJC3768).

The diazocine **112** ($R^1-R^5 = \text{H}$), first synthesized by Perlmutter (68CC1202), and derivatized and resolved by Solladié and co-workers (75S246; 78JCR(S)408) (see Section II,C,3,b), has been the subject of further stereochemical study by the latter group. The diazocine **112** ($R^1 = \text{Ac}$, $R^2-R^5 = \text{H}$) was converted into the formyl derivative **112** ($R^1 = \text{CHO}$, $R^2-R^5 = \text{H}$). This compound was optically resolved. The ΔG^\ddagger of racemization (and thus diazocine tub inversion) was 37 kcal/mol, the first genuine

racemization rate reported for a diazocine [compare with 27 kcal/mol for an eight-membered ring-substituted dibenzocyclooctatetraene (62JA3591)]. Time-dependent ^1H -NMR studies of **112** ($\text{R}^1 = i\text{-Pr}$ and PhCH_2 , $\text{R}^2\text{--R}^5 = \text{H}$) detected no rapid inversion of these molecules at 150°C (76CC276). The ^{13}C -NMR spectra of a series of substituted diazocines **112** were compared with acyclic ketimines PhC(R)=NR' . A study of the chemical shifts (i.e., substituent effects, variations of shielding and deshielding related to the magnitude of n,π and π,π interactions) confirmed the nonplanarity of the ketimines and the tub conformation (**160**) for the diazocine, similar to that for **146** (77OMR105). The twisting power (β) of a series of five optically active diazocines **112** (CHO group in positions R^1 , R^3 , or R^5) and **161** have been determined in the nematic mesophase MBBA [*N*-*p*-(methoxybenzylidene)-*p'*-butylaniline]. The twisting powers of the resulting cholesteric liquid crystal were higher than β values observed when other chiral molecules were used, suggested that if chiral and nematic structures are similar, a better intermolecular arrangement occurs, resulting in a better transmission of chirality. Interestingly, β was higher when it was attached to the fused benzo rings (78MI1).



(160)



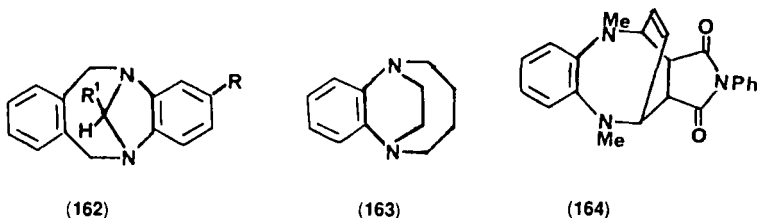
(161)

IV. Reactions

A. EIGHT-MEMBERED RING-PRESERVED ANNELATIONS

Sprake and co-workers reacted the dibenzodiazocines **89** ($\text{R} = \text{H}$, $\text{R}' = \text{H}$, Cl , OMe , CF_3) with formaldehyde and aromatic aldehydes to yield the methano-bridged compounds **162**. A number of ketones failed to react. Also, the nitro derivative **89** ($\text{R} = \text{H}$, $\text{R}' = \text{NO}_2$) failed to react with aldehydes (69JCS(C)882; 70JCS(C)1161). Yale and Spitzmiller reported similar reactions of **89** ($\text{R} = \text{R}' = \text{H}$) with an aliphatic aldehyde and several aromatic aldehydes to give **162** [$\text{R} = \text{H}$, $\text{R}^1 = \text{Et}$, $p\text{-ClC}_6\text{H}_4$, $o\text{-ClC}_6\text{H}_4$,

3,4,5-(OMe)₃C₆H₂, *p*-(Et₂NCH₂CH₂O)C₆H₄ (76JHC443)]. The benzo-1,4-diazocines **86** (R = Ac, Ts) were converted to the benzodiazabicyclo[4.2.2]decan **163** by successive hydroxyethylation and cyclization (81KGS1538). Diazocine **53** (R = Me) was reported to react rapidly with *N*-phenylmaleimide to afford Diels–Alder adduct **164** (71TL2437).



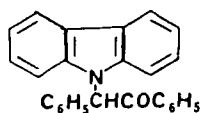
B. EIGHT-MEMBERED RING-PRESERVED DEFUNCTIONALIZATIONS, FUNCTIONALIZATIONS, REDUCTIONS, AND OXIDATIONS

N-Defunctionalization (N-desulfonation, carbonyl reduction, etc.) has been routinely employed to obtain parent diazocines from the initially prepared substituted derivatives such as *N*-tosyl compounds and lactams (see Section II,C). Examples include hydrolysis of *N*-tosyldiazocines (53CB197, 53CB380; 63ZC465; 65JOC43; 67JOC3270; 69JCS(C)882; 70JCS(C)1161, 70USP3496164; 72JCS(P1)1964; 74MI1; 82CZP195226), deacylation of *N*-acyldiazocines (70USP3496164; 74GEP2334783; 76JHC443; 79AG1028; 80CB3161), *N*-debenzylation (71JCS(C)1354), and dehydration of a hydroxydiazocine (77H273).

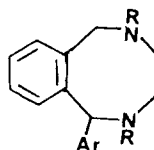
Functionalizations include *N*-sulfonation (67JOC3270), *N*-acylations (67BRP1093064; 69JCS(C)882; 70JCS(C)1161; 71USP3565888; 74MI1; 76JHC443; 81KGS1538), and *N*-alkylations (63ZC465; 69JCS(C)882; 70JCS(C)1161; 74GEP2334783; 76JHC443; 81KGS1538). Reductions include transformation of *N*-acyl to *N*-alkyldiazocine (67BRP1093064), lactam–amine conversions (71BCJ478, 71CJC2023; 76JHC475), and diazacyclooctadiene– or diazacyclooctene–diazacyclooctane conversions (67IZV1829; 67JOC3270). A hexahydrobenzodiazocine has been dehydrogenated to a tetrahydrobenzodiazocine (67JOC3270). A titanium tetrachloride-induced functionalization of dibenzodiazocinedione **57** (and benzene-substituted derivative) with secondary amines afforded amidines **73** (R¹ = H, Me; NR₂ = 4-methyl-1-piperazinyl, 4-morpholinyl, 4-carbethoxy-1-piperazinyl) (85H1425) (see Section II,C,1 and II,C,3b).

C. RING CONTRACTIONS

Ring contractions of 1,4-diazocines have led to a number of different types of products. Lithium aluminum hydride reduction of dibenzodiazocine **91** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) resulted in formation of carbazole **165** (59JOC306). When benzodiazocine **166** ($R = \text{Me}$, $\text{Ar} = p\text{-ClC}_6\text{H}_4$) was heated with acetic anhydride, the isoindole **167** was formed (70CJC1670). Acid-catalyzed detosylation of the dibenzodiazocines **15** [$R = \text{H}$, Me , $(\text{CH}_2)_2\text{NMe}_2$, $(\text{CH}_2)_3\text{NMe}_2$] resulted in an unexpected ring contraction to produce phthalimidines **168**. In addition, **15** ($R = \text{Me}$) reacted with phenyllithium to



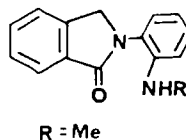
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(166)



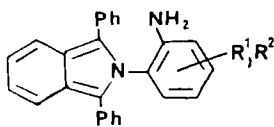
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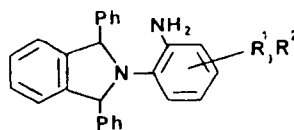
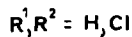
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afford a 3-phenyl-substituted **168** (JCS(P1)1964). Diborane reduction of the dibenzodiazocines **112** ($R^1 = R^2 = \text{H}$ or Cl ; $R^3 - R^5 = \text{H}$) resulted in formation of isoindole **169** and dihydroisoindoles **170** (75T1911).

A number of 1,4-diazocines have reacted to form imidazoles and fused-ring analogs. Beckmann rearrangement of the dioxime **171** yielded isoindolo-benzimidazole **172** ($R^1 = \text{Cl}$, $R^2 = \text{H}$) or **172** ($R^1 = \text{H}$, $R^2 = \text{Cl}$), most likely via rearrangement of an initially formed dichloro- **57** (57JCS1900). Dibenzodiazocinedione **57**, when heated with phosphorus pentachloride, afforded an



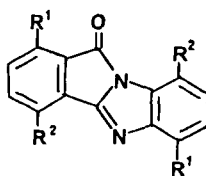
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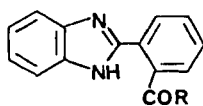


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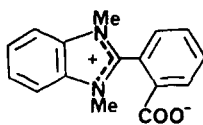


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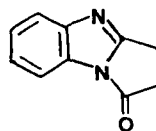
unstable material that gave the substituted 2-phenylbenzimidazole **173** ($R = \text{OMe}$) on treatment with methanol. Alkaline hydrolysis of **57** yielded **173** ($R = \text{OH}$). N,N' -Dimethylation of **57**, followed by hydrolysis, gave the zwitterionic **174**. Thermolysis of **57** yielded **172** ($R^1 = R^2 = \text{H}$), whereas similar treatment of benzodiazocine **69** ($R = \text{H}$) afforded benzimidazopyrrole **175** (69JOC2138). Identical results were reported when **57** was treated with



(173)



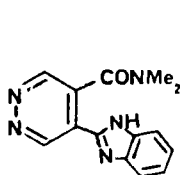
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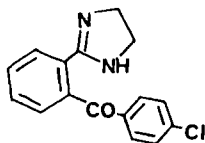
(175)

phosphorus oxychloride, followed by N -methylpiperazine and methanol to give **173** ($R = \text{OMe}$, and $R = N$ -methylpiperazinyl, respectively). The titanium(IV)-induced conversion of **57** to **73** (*vide supra*) also afforded substituted benzimidazoles **173** ($R = N$ -methylpiperazinyl) when methyl- and nitro-substituted **57** was used, the benzimidazole being the only product when nitro-substituted **57** was used (85H1425).

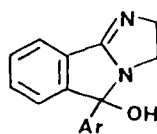
Heating pyridazinobenzodiazocine **74** with hexamethylphosphoramide afforded benzimidazolylpyridazine **176** (74JCS(P1)1022). Treatment of a hydrochloric acid solution of benzodiazocine **166** ($R = \text{H}$, $\text{Ar} = p\text{-ClC}_6\text{H}_4$) with potassium permanganate afforded phenylimidazole **177** (69FRP1580184; 70FRP7457). On the other hand, **166** ($R = \text{H}$) could be oxidized to hydroxyisindolobenzimidazole **178** (75USP3885037; 75USP3898231).



(176)

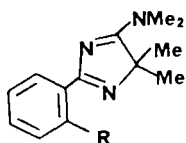


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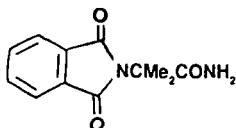


(178)

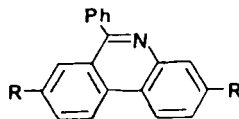
As mentioned earlier (see Section II,C,3,b), irradiation of the benzo-cyclobutaquinoxaline **56** resulted in formation of isoindolobenzimidazole (**96**), presumably via ring contraction of diazocinyl radical **104** followed by reaction with solvent (70JOC1228). The 2,5-benzodiazocine derivative **127** undergoes ring contraction in alcoholic solvents to give imidazolyl benzoate **179** ($R = \text{CO}_2\text{Me}, \text{CO}_2\text{Et}$), in water to yield the benzoic acid **179** ($R = \text{CO}_2\text{H}$), and in alcoholic solutions containing dimethylamine or pyrrolidine to afford benzamides **179** [$R = \text{CONMe}_2, \text{CON}(\text{CH}_2)_4$]. Sodium borohydride reduction of **127** afforded the benzyl alcohol **179** ($R = \text{CH}_2\text{OH}$) and phthalimide **180** (77HCA2476). Upon heating, dibenzodiazocines **91** ($R^1 = \text{Ph}, R^2 = \text{H}, \text{CO}_2\text{H}, \text{CO}_2\text{Me}, R^3 = \text{H}$) undergo ring contraction to phenanthridines **181** ($R = \text{H}, \text{CO}_2\text{H}, \text{CO}_2\text{Me}$) and benzonitrile (63JOC4290).



(179)

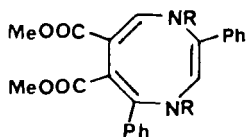


(180)

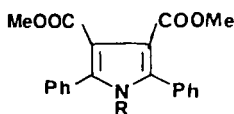


(181)

In a study of pericyclic reactions, Lown *et al.* reported that dihydropyrazines reacted with DMAD to yield a series of dihydroazetidinopyridinedicarboxylates that were formed by reversible ring contraction of diazocines **54**. One of the latter compounds (**54**, $R = \text{sec-Bu}$) was actually isolated by thermolysis of the corresponding azetidinopyridine **55** ($R = \text{sec-Bu}$) (see Section II,B,4). Thermolysis or photolysis of **55** proceeded sequentially via diazocines **54** and π -rearranged diazocine **182** (never isolated). The products formed were pyrroles **183**, phenylacetone nitriles **184**, and phenylketeneimines **185** (isolated as the hydrolysis product, phenylacetamides **186**, and trapped with thiophenol as the pseudothiurea **187**). In one instance (**54**, $R = t\text{-Bu}$), the keteneimine was actually isolated during photolysis of **55**. The above reactions were also run with chiral R groups and the predicted orbital-symmetry-allowed stereochemistry was found for thermolysis and photolysis reactions (75JOC3363).



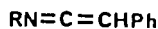
(182)



(183)



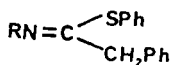
(184)



(185)



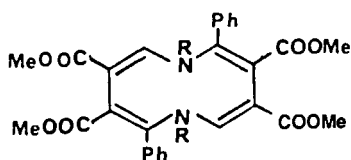
(186)



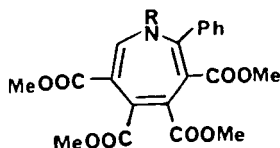
(187)

D. RING EXPANSIONS

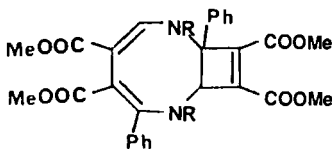
Lown *et al.* found that azetidinopyridines **55** ($\text{R} = t\text{-Bu}, \text{sec-Bu}$) undergo a thermal reaction with either 1 equivalent or an excess of DMAD to give 10-membered diazecines **188** ($\text{R} = t\text{-Bu}, \text{sec-Bu}$). Compound **55** ($\text{R} = \text{sec-Bu}$) also produces azepine **189**. The 10-membered heterocycle was said to arise from addition of DMAD to **182** to afford a cyclobutenodiazocine, one of the possible intermediates being **190**. It is possible that azepine **189** arose by similar intermediacy of diazocine **54** (75JOC3363).



(188)



(189)

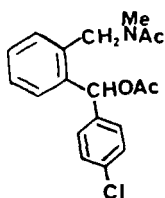


(190)

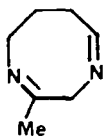
E. RING-OPENING REACTIONS

The 1,4-diazocinedione **31** (admixed with a much larger amount of isomeric 1,5-diazocinedione) was hydrolyzed in aqueous acid to give glycine and γ -aminobutyric acid, whereas hydrolysis of the triazolo derivative **32**, mixed with its 1,5-diazocine isomer, afforded only γ -aminobutyric acid (65BSF691). Dibenzodiazocine **112** ($\text{R}^1-\text{R}^5 = \text{H}$) (see Section II,C,3,b) was hydrolyzed to

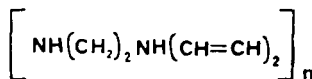
OPD and *o*-dibenzoylbenzene (68CC1202). Benzodiazocine **166** ($R = \text{Me}$, $\text{Ar} = p\text{-ClC}_6\text{H}_4$), upon treatment with acetic anhydride, yields, in addition to isoindole **167** (*vide supra*), the benzhydryl **191** (70CJC1670). Mild alkaline hydrolysis of pyridazinobenzodiazocine **74** yielded 5-(*o*-aminophenyl-carbamoyl)pyridazine-4-carboxylic acid (74JCS(P1)1022). The diazocine **192** or its saturated derivative, when condensed with diacetylene in dry benzene or without a solvent, gave heterochain polyamine **193** (70MI1).



(191)



(192)

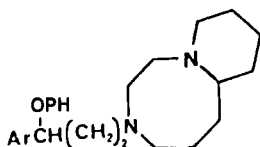


(193)

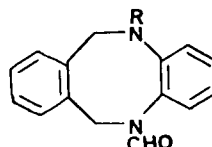
V. Applications

The diazocine **9** is among some cyclic diaza compounds that are useful as anthelmintic, germicidal, and adrenolytic agents, and that find use as accelerators for rubber manufacture (64FRP1378964; 66USP3247206). The lactams **122** find use as corrosion inhibitors for metals and as bacteriocides (80MIP1; 81JAP81-154468, 81MI1), whereas **122** ($R^3 = \text{H}$) exhibited varying therapeutic effects in mammals as central nervous system (CNS) depressants, as stimulants, and as antiinflammatory agents (66USP3293243). Bisactams such as ethylene succinamide have found use as dyes or pharmaceutical intermediates (39USP2156300).

Substituted benzo-2,5-diazocines **7** have frequently been synthesized for their pharmacological properties—some of these are unspecified therapeutic agents (67FRP1487344), anorectics (appetite depressants), CNS stimulants (67MI1, 67MI2, 67NEP6614399; 70USP3499806; 71USP3565888; 72USP3663532; 76USP3994920), analgesics, antitussives, antipyretics (83EUP89743), anticonvulsants and/or anorectics, and/or antitemorine agents and/or CNS depressants (67BRP1093064; 70USP3496164). Also sharing this latter group of properties are the lactams **117** (64BEP646221). The piperidinodiazocine **194** was reported to be an antitussive or antihistamine (74JAP74-28755). The dibenzodiazocines **195** were useful as CNS depressants (74GEP2334783) or stimulants (74GEP2334782; 76JHC443). The (diazocinyl)imidazobenzothiadiazepine **196** was prepared as a tranquilizer (80EUP42354).

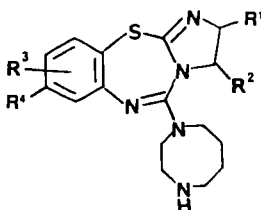


(194)



R = various

(195)



(196)

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Recent Advances in Azomethine Ylide Chemistry

OTOHIKO TSUGE AND SHUJI KANEMASA

*Institute of Advanced Material Study, Kyushu University,
Kasugakoen, Kasuga 816, Japan*

I. Introduction	232
II. Generation	233
A. Aziridine Route	234
B. Desilylation Route	239
C. Tautomerization Route	249
D. Deprotonation Route	256
E. Decarboxylation Route	269
F. N-Oxide Route	277
G. N-Metallation Route	280
H. Oxazoline Route	287
I. Miscellaneous Routes	292
III. Cycloadditions	295
A. Reactivity of Ylides	295
1. Unsymmetrical Activated Olefins and Acetylenes	295
2. Nonactivated Olefins and Acetylenes	298
3. Carbonyl Compounds and Imines	301
4. Other Carbon-Hetero Double Bonds	304
5. Nitrogen-Nitrogen Multiple Bonds	305
B. Geometry of Ylides	306
1. Ylides from the Aziridine Route	306
2. Ylides from the Tautomerization Route	309
3. Ylides from the Deprotonation Route	310
4. Ylides from the Decarboxylation Route	311
5. Ylides from the N-Metallation Route	313
C. Stereoselectivity	314
1. Cycloadditions to Cyclic <i>cis</i> -Olefins	315
2. Cycloadditions to Symmetrical Acyclic Olefins	319
D. Regioselectivity	319
E. Regio- and Stereoselective Cycloadditions	327
IV. Intramolecular Cycloadditions	333
A. Ylides from the Aziridine Route	333
B. Ylides from the Tautomerization Route	335
C. Ylides from the Deprotonation Route	336
D. Ylides from the Decarboxylation Route	337
V. Natural Product Synthesis	337
A. Utilization of Intermolecular Cycloadditions	338
B. Utilization of Intramolecular Cycloadditions	340
VI. Conclusion	343
References	344

I. Introduction

Azomethine ylides are planar molecules composed of one nitrogen and two terminal sp^2 carbons. At most, four geometrical isomers are possible for these transient molecules. Their cycloadditions to olefin or acetylene dipolarophiles give rise to the formation of two sets of carbon-carbon bonds in a single step. Because of the structural complexity of azomethine ylide itself compared to other dipoles and the stereochemical selectivity in the cycloadditions, a number of stereoisomers are possible for the cycloadducts. These two points make azomethine ylides one of the most attractive 1,3-dipoles, both in the fields of ylide chemistry and synthetic organic chemistry.

The cycloadditions to olefin dipolarophiles provide pyrrolidine derivatives that are the central skeletons of numerous alkaloids. As a variety of azomethine ylides are readily available and these cycloadditions proceed with a high stereochemical selectivity, the synthetic versatility of azomethine ylides is multiplied. Accordingly, the following must be important points in a study on the chemistry of azomethine ylides: (1) an effective generation of a wide variety of azomethine ylides from readily available starting materials, (2) high reactivity of each ylide to various olefin dipolarophiles, (3) full understanding of the geometry of azomethine ylides that are concerned in the cycloadditions to a dipolarophile, and (4) an answer to the question of the selectivity-determining factors in a cycloaddition step.

In the late 1970s investigations of azomethine ylides focused mainly on heteroaromatic N-ylides and highly stabilized ylides, because the only practical preparation method of azomethine ylides available at that time was either the deprotonation of iminium salts or the thermal ring opening of aziridines. Deprotonation of the salts of nitrogen heteroaromatics such as pyridine, quinoline, isoquinoline, and thiazole was widely used to generate a number of heteroaromatic N-ylides, and this route is still the most effective and general access to these dipoles (76MI1). Thermal ring opening of aziridines was a nice way to the azomethine ylides stabilized by at least one electron-withdrawing substituent.

Like other 1,3-dipoles, azomethine ylides were mostly utilized in the ring construction of five-membered nitrogen heteroaromatics by a sequence of cycloadditions to acetylenes and formal oxidation. Thus, azomethine ylides were employed as the synthetic equivalents of nitrile ylides. Other synthetic applications of azomethine ylides, especially the intended utilization of stereochemical characteristics of the azomethine ylide cycloadditions, were quite rare.

Since 1978, azomethine ylide 1,3-dipoles have been more intensely studied than any other dipoles, and the chemistry of azomethine ylides has made

remarkable progress. As the outset of this flourishing chemistry we probably have to go back to the two pioneering works made by Vedejs (79JA6452) and Grigg (78CC109). The desilylation access discovered by Vedejs has demonstrated that nonstabilized azomethine ylides, the ylides bearing no ylide-stabilizing substituents, can be smoothly generated if an appropriate method is employed, and that these ylides have considerable stability and high reactivity to a variety of dipolarophiles. It was accordingly 1979 when the chemistry of nonstabilized azomethine ylides started. Although an imine-azomethine ylide tautomerism was known in the case of several azalactones (70CB2356, 70CB2368, 70JA4340), the tautomerization access discovered by Grigg has increased the synthetic versatility of ester-stabilized azomethine ylides because of their ready accessibility as well as the high stereoselectivity in their cycloadditions. This method was eventually developed to the more widely applicable ylide generation through a deprotonation or a decarboxylation process.

Azomethine ylides can be classified in groups according to their structure. Acyclic azomethine ylides have an open-chain structure, and even if part or the whole of ylide conjugation is included in a nonconjugated ring system, such ylides can also be regarded as acyclic types. When part or the whole of ylide conjugation is included in a conjugated heterocycle, such azomethine ylides belong to the class of heteroaromatic N-ylides, mesoionic azomethine ylides, or aromatic betaines.

Most previous reviews on azomethine ylides have dealt with these ylides all together (73S469; 76T2165; 80AG979; 84MI1). However, we concentrate on the most basic ylides, acyclic azomethine ylides, in order to catch the generalized concepts involved in the azomethine ylide chemistry. Accordingly, this article deals with the recent advances of the chemistry of acyclic azomethine ylides. For readers deeply interested in other types of azomethine ylides, there are excellent reviews (76MI1; 84H2079, 84MI2). The major sections of this article cover the preparation, cycloadditions, intramolecular cycloadditions, and synthetic applications of acyclic azomethine ylides.

II. Generation

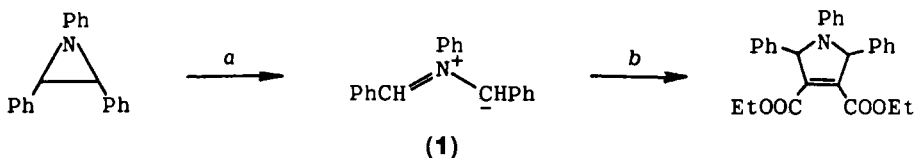
There are two general concepts for the generation of azomethine ylide 1,3-dipoles. The most fundamental is ylide generation by the elimination of a positively charged group at the α -position of iminium salts. The group being eliminated may be a silyl cation (R_3Si^+), proton (H^+), or proton and carbon dioxide ($H^+ + CO_2$). The second generation pattern involves the (valence) tautomerization of isolable (valence) isomers of azomethine ylides.

As described above, the only practical generation method of acyclic azomethine ylides known in the late 1970s was the thermal ring opening of aziridines. This belongs to the valence tautomerization approach. Since then, several new methodologies have been developed. However, there are no comprehensive reviews on these ylide generations. Even the latest review presents only a few (84MI2). Therefore, it will be useful to summarize all of the generation methods of acyclic azomethine ylides, including the aziridine route. The generation methods reported are divided into groups according to the concept used for the ylide generation, and structures of the azomethine ylides available by each generation route are tabulated.

Of these new methodologies, some have been reviewed by Grigg on the tautomerization approach (84BSB593; 87CSR89), and by Achiwa (85YGK862) and Vedejs (86CRV941) on the desilylation approach.

A. AZIRIDINE ROUTE

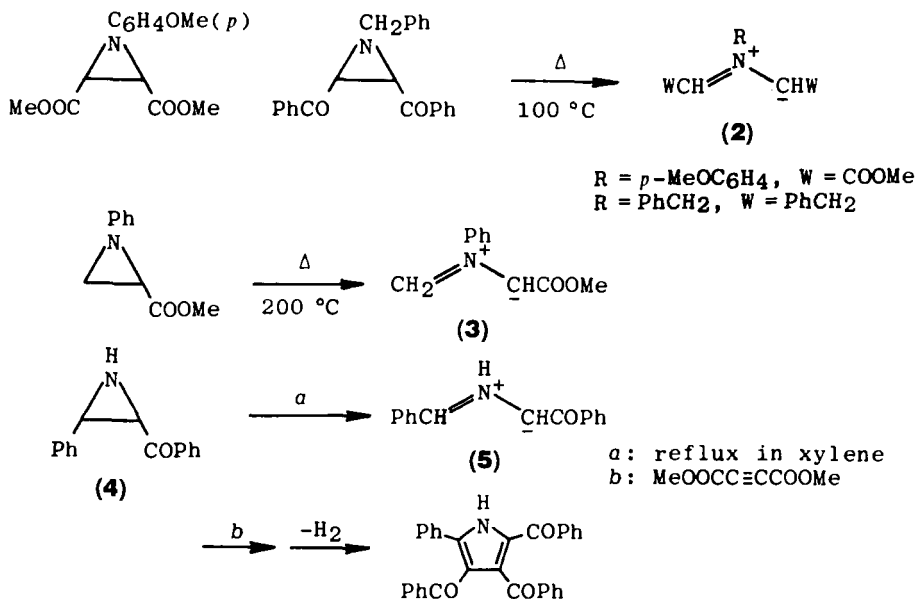
As early as 1965, the first example of the the carbon-carbon bond cleavage of an aziridine generating an azomethine ylide 1,3-dipole was reported by Heine and Peavy (65TL3123). This also offers the first generation of acyclic azomethine ylides by the *aziridine route*. Thus, 1,2,3-triphenylaziridine, with its stereochemistry unspecified, was heated under reflux in toluene in the presence of diethyl acetylenedicarboxylate. The azomethine ylide (**1**) generated was captured by the acetylene to give a quantitative yield of diethyl 1,2,5-triphenyl-3-pyrroline-3,4-dicarboxylate.



a: reflux in toluene
b: EtOOC≡CCOEt

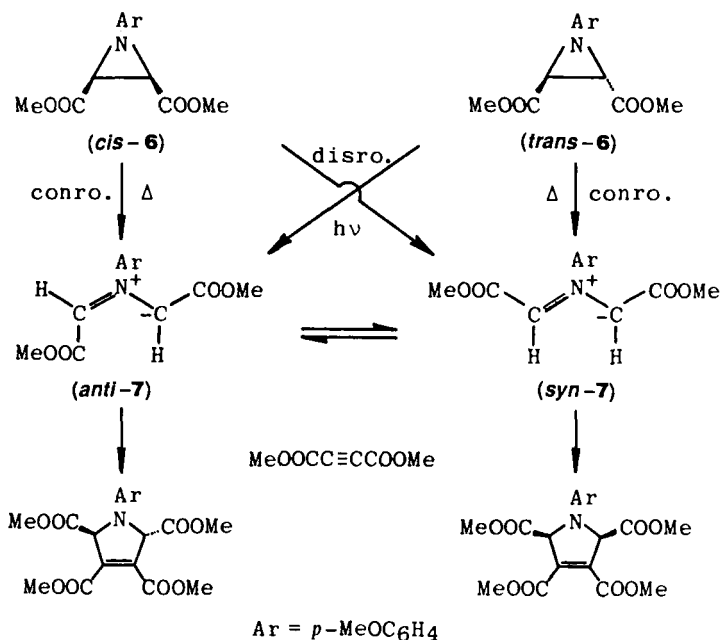
Padwa (65TL4363) and Huisgen (66TL397) obtained similar results independently, a little later than Heine. Aziridine rings open quite readily if the carbon atoms are substituted by electron-withdrawing substituent(s) because the electron-rich ylide centers of the resulting azomethine ylides are stabilized by such substituents. Thus, the aziridines bearing two ester or benzoyl moieties on the carbon generate ylides **2** at only 100°C. The aziridine bearing one ester activating group as the only C substituent undergoes ring opening to generate azomethine ylide **3** at 200°C (66TL397). This indicates that a single ylide-stabilizing substituent is effective enough to open the aziridine ring when it is more electron withdrawing than an ester moiety

(85JOC2309, 85TL3747). It is interesting that an N-H aziridine (**4**) generated N-unsubstituted azomethine ylide **5**, which cycloadded to dimethyl acetylenedicarboxylate to afford a pyrrole after a spontaneous dehydrogenation (65TL4363). Formation of neither the Michael-type adduct between aziridine **4** and the acetylene (65JOC1298) nor the tautomeric imine of ylide **5** indicates the considerable stability of N-unsubstituted azomethine ylide **5**. The stability of N-unsubstituted azomethine ylides is discussed in Section II,B.



Huisgen was the first to explain the stereochemical course of azomethine ylide generation by the aziridine route (67JA1753). He applied the rules of conservation of orbital symmetry, discovered by Woodward and Hoffmann (65JA395), to the thermal and photochemical ring opening of *cis*- and *trans*-aziridine-2,3-dicarboxylates **6**. Stereospecific ring cleavage of *cis*-**6** or *trans*-**6** generates each isomeric azomethine ylide **7**, which then is trapped by dimethyl acetylenedicarboxylate in a stereospecific fashion. Thermal ring opening of *cis*-**6** or *trans*-**6** takes place in a conrotatory manner, leading to azomethine ylide *anti*-**7** or *syn*-**7**, respectively. Photolysis results in a disrotatory ring cleavage, aziridine *cis*-**6** or *trans*-**6** being transformed into ylide *syn*-**7** or *anti*-**7**, respectively. Isomerization between *anti*-**7** and *syn*-**7** takes place if the ylide is not trapped immediately after its generation.

Stereochemical studies on the ring-opened azomethine ylide 1,3-dipoles thermally or photolytically generated from sterically defined aziridines are important in order to learn the geometry of transient ylide species. Though the aziridine route has a limitation in that an appropriate ylide-stabilizing



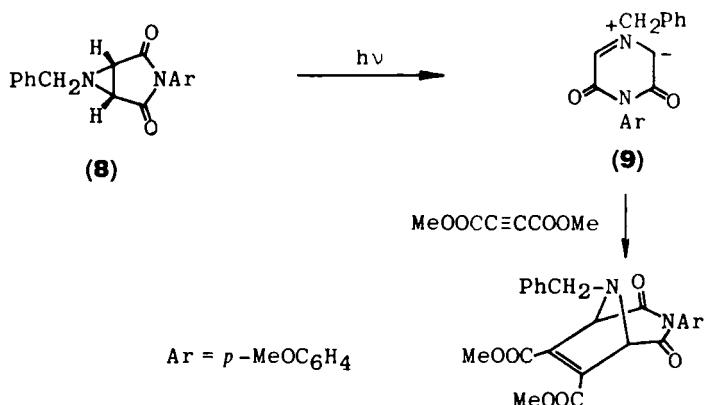
substituent is required for the smooth ring opening of aziridines, this route was the only one, until quite recently, in which ylide generation could be discussed from the viewpoint of stereospecificity (70JOC888; 71CC1187, 71CC1188, 71JA1779).

Isomerization between a *syn*-azomethine ylide and an *anti*-isomer is often observed even when a reactive dipolarophile, such as acetylenedicarboxylate, is employed in intermolecular trapping (67JA1753; 70JOC888; 71CC1187, 71CC1188, 71JA1779). The *syn-anti* isomerization of less stabilized azomethine ylides has been discussed in an intramolecular trapping experiment (79JOC255).

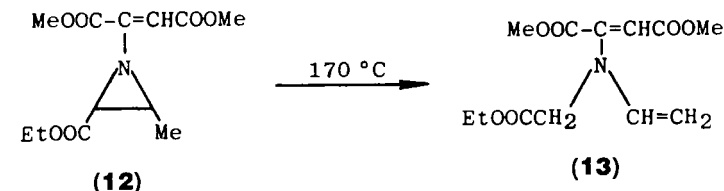
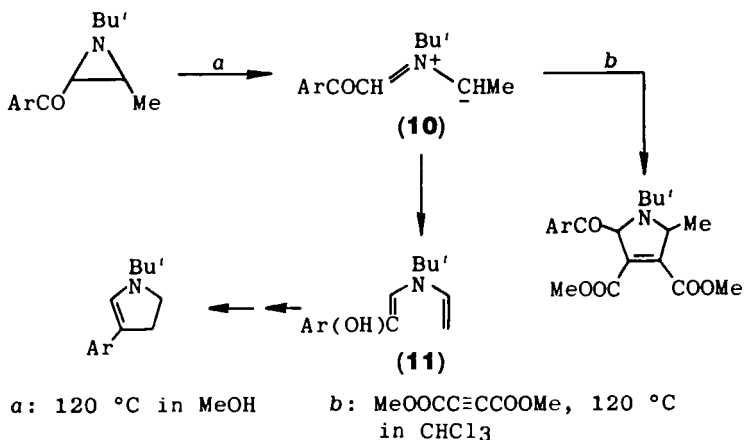
When an aziridine ring is fused at the 2,3-bond to another ring system, the only ring opening structurally allowed is a disrotatory rotation, which must be photolytically performed as discussed above. Thus, the fused aziridine **8** on irradiation generates *syn*-azomethine ylide **9**, which is captured by an acetylene to give a bicyclic cycloadduct (68CPB764).

Other types of ring-fused aziridines, fused at the 1,2-bond, similarly generate azomethine ylides whose skeleton is partially incorporated in a ring system (68JOC1097; 69JOC171; 86JCS(P1)1119).

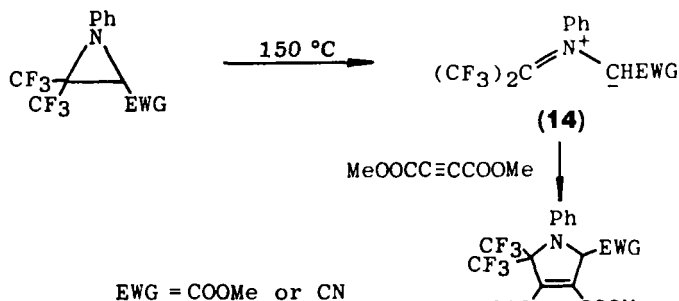
When the aziridine bearing an acyl moiety on one carbon and a methyl on the other is heated in a protic solvent, the ring-opened azomethine ylide **10** rearranges into an enolated bisenamine intermediate **11**, which undergoes



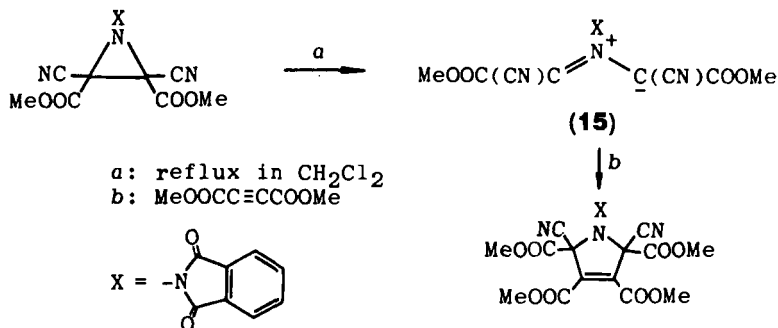
cyclization to give a pyrrole derivative (75JA2822). Later, the closely related rearrangement of 1-vinyl-2-methylaziridine **12** into a bisenamine **13** was observed, confirming the proposed mechanism for the above reaction (82CJC2830). However, such a rearrangement does not necessarily become a serious restriction in generating azomethine ylides with a substitution pattern of C(1)—COR and C(2)—CH₂R'. Azomethine ylide **10** can be quantitatively trapped by dimethyl acetylenedicarboxylate prior to its rearrangement, when generated in an aprotic solvent.



The aziridine route has rarely found application to the generation of azomethine ylides substituted by at least one alkyl moiety on carbon because alkyl groups are incapable of stabilizing the ylide center of azomethine ylides. However, thermolysis of 1,1-bis(trifluoromethyl)aziridines provides good access to trifluoromethyl-substituted azomethine ylides **14** (76T1995).

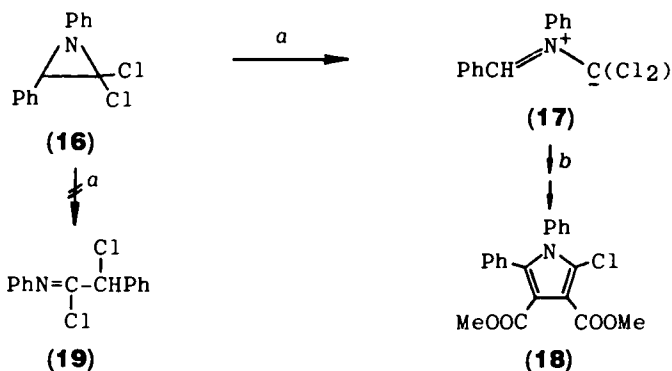


Generation of azomethine ylides with a hetero substituent on the nitrogen has been demonstrated by the thermolysis of 1-phthalimidoaziridines, leading to the corresponding *N*-aminoazomethine ylides **15** (83JOC481). This reaction occurs even at the boiling temperature of dichloromethane.



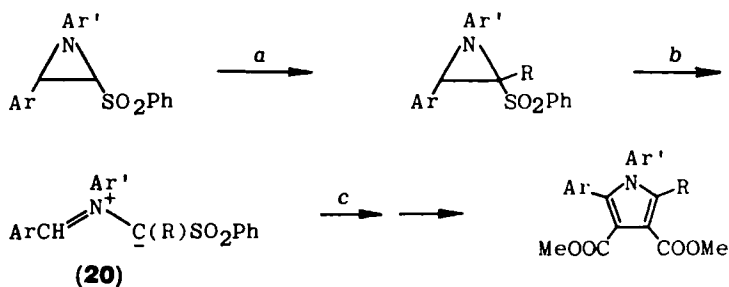
Few examples are known for the generation of C-heterosubstituted azomethine ylides by the aziridine route. Interesting is the thermolysis of 2,2-dichloroaziridine, readily accessible by the reaction of an imine with dichlorocarbene (81JOC2079). Thermolysis of **16** in the presence of dimethyl acetylenedicarboxylate gave pyrrole **18** by the cycloaddition of intermediate 1,1-dichlorinated azomethine ylide **17** (84JCR(S)82). None of the usual thermolysis product, 2-chloroacetimidoyl chloride (**19**), was obtained (78JOC1346).

A sulfonyl substituent at the carbon of aziridines stabilizes the ring anion so that an alkyl moiety can be introduced at this position. As the ring is activated by the sulfonyl group, alkylated aziridines undergo a ready ring

a: reflux in C₆H₆

b: MeOOC≡CCOOMe

opening leading to sulfonyl-substituted azomethine ylides **20**. After the cycloaddition with an acetylene, the sulfonyl group acts as leaving group to give pyrrole derivatives (84TL1949).



a: LDA, -78 °C in THF + RX, r.t.

b: 100 °C

c: MeOOC≡CCOOMe

Table I summarizes the azomethine ylide 1,3-dipoles that have been generated by the aziridine routes.

B. DESILYLATION ROUTE

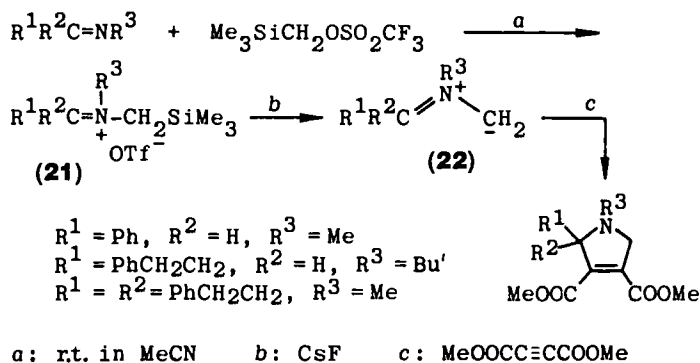
In 1979 Vedejs and Martinez reported a terse communication on a new concept for the generation of nitrogen, sulfur, and phosphorus ylides. Their method consists of initial alkylation of the heteroatom of amines, imines, sulfides, or phosphines with trimethylsilylmethyl triflate, and subsequent desilylation of the resulting salts with fluoride ion (79JA6452). For the

TABLE I
AZOMETHINE YLIDES GENERATED BY THE "AZIRIDINE ROUTE"

Azomethine ylides $[R^1R^2C=NR^+-C^--R^3R^4]$					
R^1	R^2	R^3	R^4	R	Reference
COOMe	CN	COOMe	CN	Phthalimido	83JOC481
CN	CN	CN	CN	Phthalimido	83JOC481
COPh	H	COPh	H	PhCH ₂	66TL397
COOMe	H	COOMe	H	<i>p</i> -MeOC ₆ H ₄	66TL397; 67JA1753; 71JA1779
COOMe	H	COOMe	Me	Me	74CC258
COOMe	COOMe	Ph	H	Ph	69TL823; 71TL4163; 78T1153
COOEt	COOEt	Ph	H	Ph	69TL823; 78T1153
COOMe	CN	Ph	H	Ph	69TL823
COOMe	CN	Ph	H	Phthalimido	83JOC481
COOMe	CN	<i>p</i> -MeOC ₆ H ₄	H	Phthalimido	83JOC481
COOMe	CN	<i>p</i> -MeC ₆ H ₄	H	Phthalimido	83JOC481
COOMe	CN	<i>p</i> -C ₆ H ₄	H	Phthalimido	83JOC481
COOMe	CN	<i>p</i> -NO ₂ C ₆ H ₄	H	Phthalimido	83JOC481
COOEt	CN	Ph	H	Ph	69TL823
COOEt	CN	Ph	H	<i>p</i> -MeOC ₆ H ₄	69TL823
COOEt	CN	Ph	H	<i>p</i> -NO ₂ C ₆ H ₄	69TL823
COOEt	CN	<i>p</i> -MeOC ₆ H ₄	H	Ph	69TL823
COOMe	CN	Me	H	Ph	69TL823
$R^1 = COOEt, R^2R = C(COOEt)=NCH(R^3), R^3 = Ph, R^4 = H$					86JCS(P1)1119
$R^1 = COOEt, R^2R = C(COOEt)=NCH(R^3), R^3 = o\text{-MeC}_6\text{H}_4, R^4 = H$					86JCS(P1)1119
$R^1 = COOEt, R^2R = C(COOEt)=NCH(R^3), R^3 = o\text{-PhCH}_2\text{C}_6\text{H}_4, R^4 = H$					86JCS(P1)1119
$R^1 = COOEt, R^2R = C(COOEt)=NCH(R^3), R^3 = o\text{-(i-Pr)C}_6\text{H}_4, R^4 = H$					86JCS(P1)1119
$R^1 = COOEt, R^2R = C(COOEt)=NCH(R^3), R^3 = 1\text{-fluorenyl}, R^4 = H$					86JCS(P1)1119
CONH ₂	CN	Ph	H	Ph	69TL823
$R^1R^3 = CON(p\text{-MeOC}_6\text{H}_4)CO, R^2 = R^4 = H, R = PhCH_2$					68CPB764
CN	CN	Ph	H	Ph	69TL823
CN	CN	Ph	H	<i>p</i> -MeOC ₆ H ₄	69TL823
PhCO	H	Ph	H	Me	68CC1543

PhCO	H	Ph	H	<i>i</i> -Pr	68CC1543
PhCO	H	Ph	H	<i>c</i> -Hex	67JHC118; 68CC1543
PhCO	H	<i>p</i> -MeOC ₆ H ₄	H	<i>c</i> -Hex	68CC1543
PhCO	H	<i>m</i> -NO ₂ C ₆ H ₄	H	<i>i</i> -Pr	75JCS(P1)1326
PhCO	H	<i>m</i> -NO ₂ C ₆ H ₄	H	<i>c</i> -Hex	68CC1543
<i>p</i> -MeC ₆ H ₄ CO	H	Ph	H	<i>i</i> -Pr	68CC1543
<i>p</i> -MeC ₆ H ₄ CO	H	Ph	H	<i>c</i> -Hex	68CC1543
<i>p</i> -NO ₂ C ₆ H ₄ CO	H	Ph	H	<i>c</i> -Hex	68CC1543
PhCO	H	Ph	H	H	65TL4363; 67JHC118
PhCO	H	<i>p</i> -NO ₂ C ₆ H ₄	H	H	68JOC1097
PhCO	H	Me	H	<i>t</i> -Bu	75JA2822
PhCO	H	CF ₃	CF ₃	Ph	76T1995
COOMe	H	Ph	H	<i>i</i> -Pr	78T1153
COOMe	H	Ph	H	<i>c</i> -Hex	78T1153
COOMe	H	<i>p</i> -PhC ₆ H ₄	H	<i>i</i> -Pr	70JOC888; 79JOC255
COOMe	H	<i>p</i> -PhC ₆ H ₄	H	<i>c</i> -Hex	70JOC888
COOEt	H	Ph	H	Ph	78T1153
COOEt	H	CF ₃	CF ₃	Ph	76T1995
COOMe	H	H	H	Ph	66TL397
COOMe	H	H	H	<i>p</i> -MeOC ₆ H ₄	85JOC2309; 85TL3747
COOMe	H	H	H	PhCH ₂	85JOC2309
CN	H	Ph	H	PhCH ₂	86T2283
CN	H	Ph	H	<i>c</i> -Hex	86T2283
CN	H	CF ₃	CF ₃	Ph	76T1995
PhSO ₂	H	Ph	H	Ph	84TL1949
PhSO ₂	H	<i>p</i> -ClC ₆ H ₄	H	Ph	84TL1949
PhSO ₂	H	<i>m</i> -ClC ₆ H ₄	Allyl	Ph	84TL1949
PhSO ₂	H	<i>m</i> -ClC ₆ H ₄	Cinnamyl	Ph	84TL1949
R ¹ R = C(Ph)=NC(Me) ₂ , R ² = H, R ³ = <i>p</i> -NO ₂ C ₆ H ₄ , R ⁴ = H					68JOC1097
R ¹ R = C(Ph)=NC ₆ H ₄ (<i>o</i>), R ² = H, R ³ = <i>p</i> -NO ₂ C ₆ H ₄ , R ⁴ = H					69JOC171
Ph	H	Ph	H	Ph	65TL3123; 69JOC2724; 71CC1187; 71CC1188
Ph	H	Ph	H	<i>p</i> -BrC ₆ H ₄	66JOC3924
Ph	H	Cl	Cl	Ph	84JCR(S)82

generation of azomethine ylides, imines are treated with the triflate in acetonitrile at room temperature to form the corresponding iminium triflates **21**. After the formation of **21** is completed, desilylation is carried out in the same flask with cesium fluoride to generate azomethine ylides **22**, which are captured by dimethyl acetylenedicarboxylate. This general route leads to nonstabilized azomethine ylides, the ylides bearing no ylide-stabilizing carbonyl-type substituents on the carbon.

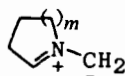
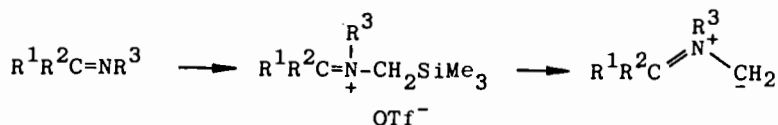
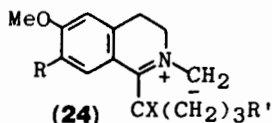
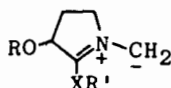
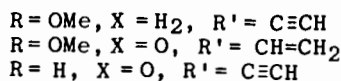
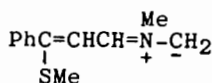


Use of trimethylsilylmethyl triflate enables the effective formation of intermediate iminium salts in the reaction mixture because the counteranion, triflate ion, is nonnucleophilic both to carbon and silicon atoms. N-Silylmethylation can also be performed with other alkylating agents, such as silylmethyl chloride, bromide, and iodide. However, the resulting iminium salts desilylate immediately after they are formed by the attack of the halide counteranions, leading to a serious decomposition of the requisite iminium intermediates. The final step of desilylation generating azomethine ylides is effected by a fluoride anion which is selectively nucleophilic to a silicon atom.

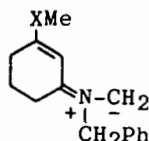
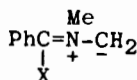
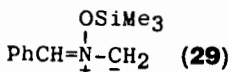
Though a sequence of N-alkylation of imines and subsequent deprotonation at the α position, instead of N-silylmethylation and desilylation, would seem to be an even more useful and general method for the generation of azomethine ylides, both the N-alkylation and the selective deprotonation are tricky processes (75JOC2048). The difficulty involved in the alkylation and deprotonation method discussed previously (86CRV941) increases the synthetic importance of the silylmethylation and desilylation method.

A number of nonstabilized azomethine ylides (**23**–**29**) have been generated by the Vedejs and Martinez method, the N-silylmethylation and desilylation sequence, using imines (82CPB3167; 83TL4303; 84JOC3314; 85T3559; 86JOC1159), imidates or thioimidates (80JA7993; 83TL4303; 84JOC3314), and an oxime (87JOC3944).

There are several preparative routes to N-silylmethyliminium salts which are the key intermediates in the Vedejs–Martinez method. Such extension

(23) $m = 1, 2$ (24) $CX(CH_2)_3R'$ (25) $X = O, S$ 

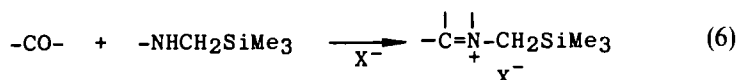
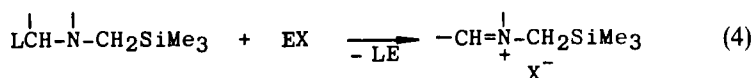
(26)

(27) $X = O, S$ (28) $X = OEt, SMe$ 

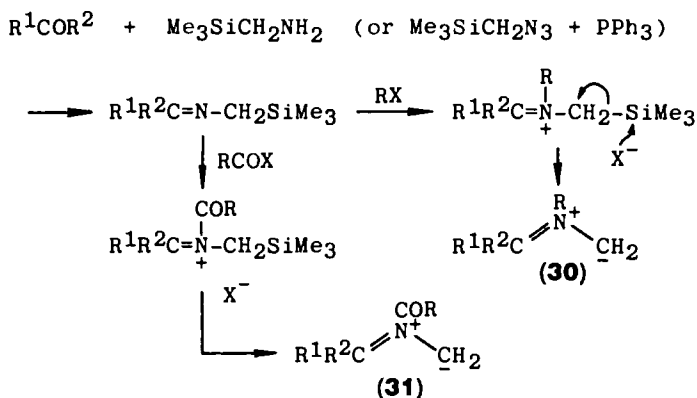
(29)

should add more synthetic versatility to the original method, so that this N-silylmethylation may be established as a general desilylation route for the generation of nonstabilized azomethine ylides. The variations are as follows: Eq. (1): N-alkylation of imines with silylmethyl triflate as discussed above; Eq. (2): quaternization of N-silylmethylamines by the addition of an electrophile (EX) to the imine nitrogen; Eq. (3): quaternization of N-silylmethylamides or related derivatives by the addition of an electrophile to the heteroatom other than the amide nitrogen; Eq. (4): quaternization of N-silylmethyl hemiacetals by the elimination of leaving group L from the adjacent carbon; Eq. (5): quaternization by the addition of an electrophile to the β -carbon of N-silylmethylenamines; and Eq. (6): condensation between secondary N-silylmethylenamines and carbonyl compounds.



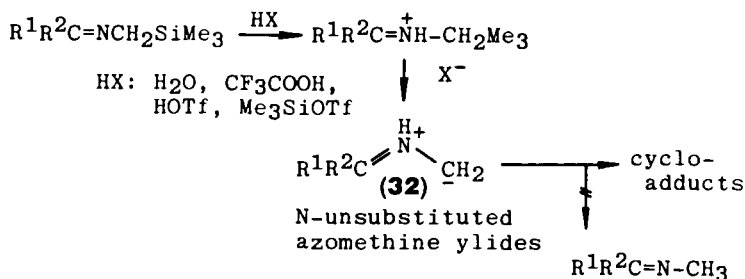


Quaternarization of N-silylmethylimines, the first variation shown in Eq. (2), is performed with electrophiles such as acyl halides (81CL1213; 83CC210, 83CPB393, 83JOC1554) and alkyl halides (83JOC1554; 84CPB2878; 85H1107, 85T3559) to generate N-alkyl- (30) or N-acylazomethine ylides 31, respectively. As the silyl moiety of the intermediate N-silylmethyliminium salts is more easily desilylated than that of the starting imines, the quaternization and desilylation steps need not be separated. An acyl or alkyl halide is simply added to N-silylmethylimines in the presence of a dipolarophile. Desilylation of the resulting iminium salts takes place spontaneously by the attack of counter halide anion X^- . Thus the quaternization method using N-silylmethylimines, shown in Eq. (2), can be carried out by a simple procedure in one flask.



As a variation of the process according to Eq. (2), the process of N-protonation of N-silylmethylimines and subsequent desilylation also works well. N-Protonated iminium intermediates are first formed and their desilylation by the counter ion (X^-) leads to N-unsubstituted azomethine ylides of nonstabilized types 32. Although the N-unsubstituted azomethine ylides 32 would be able to isomerize irreversibly into the corresponding N-methylimine tautomers, these unusual azomethine ylides show a remark-

able stability so that they may be captured by activated dipolarophiles as high yields of cycloadducts. The reagents used for the N-protonation and desilylation process are water (84CL801; 85H2489; 86BCJ2537; 87JOC2523), trifluoroacetic acid (84CL2041; 85H1107; 86CL1113), and triflic acid with cesium fluoride (87JOC2523). Such remarkable stability of N-unsubstituted azomethine ylides **32**, especially under the highly acidic conditions employed for desilylation, is quite surprising because an acid also must have catalyzed the irreversible conversion of ylides **32** to N-methylimine tautomers.



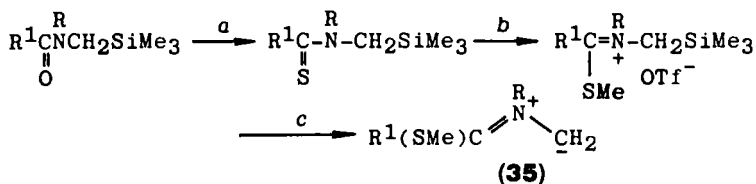
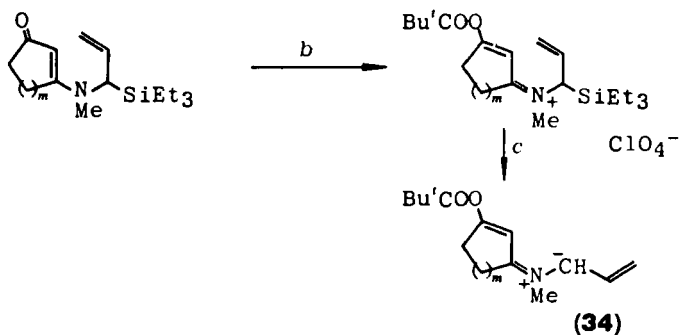
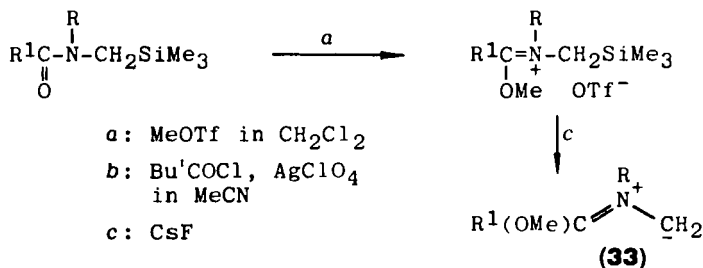
N-Silylation with trimethylsilyl triflate forms N-silylated iminium triflates, which are subsequently desilylated *in situ* with fluoride ion to generate N-silylated azomethine ylides (82TL2589; 84CL2041; 85CPB1975).

As mentioned above, the quaternarization method using N-silylmethylimines [Eq. (2)] offers an even more general and convenient method of azomethine ylide generation than the original N-silylmethylation method shown by Eq. (1). Another advantage is the ready availability of N-silylmethylimines, which are conveniently prepared by the condensation of carbonyl compounds with silylmethylamine or with silylmethyl azide in the presence of triphenylphosphine (84JOC2688).

The second variation for the generation of N-silylmethyliminium salts involves the alkylation, acylation, or silylation of N-silylmethylamides or derivatives on a heteroatom other than the amide nitrogen [Eq. (3)]. O-Alkylation of N-silylmethylamides with methyl triflate (80JA7993; 83JOC4773; 85JOC2170) or O-acylation of N-silylmethylenaminones (83JA6160) leads to N-(1-silylalkyl)iminium salt intermediates, respectively; the fluoride-induced desilylation generates azomethine ylides **33** and **34**.

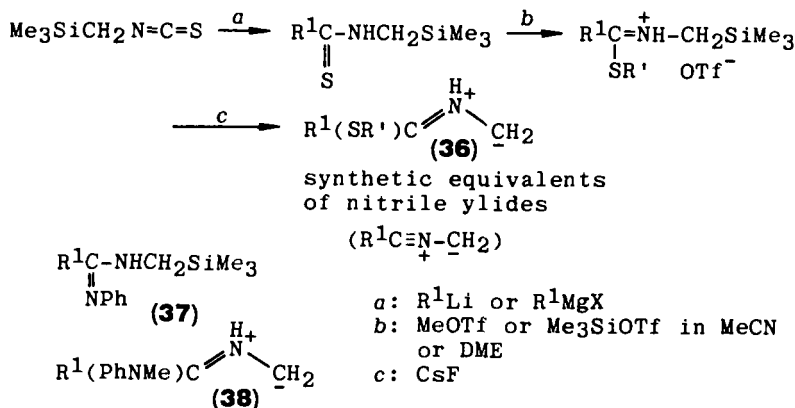
In general S-alkylation of thioamides occurs much more readily and selectively than O-alkylation of amides. Thus, N-silylmethylthioamides obtained by the reaction of N-silylmethylamides with Lawesson's reagent (83JOC4773) are treated with methyl triflate to give C-methylthioiminium triflate ylide precursors. Their desilylation with cesium fluoride generates C-hetero-substituted azomethine ylides **35** (83JOC4773; 85JOC2170).

Secondary N-silylmethylthioamides with a variety of C substituents

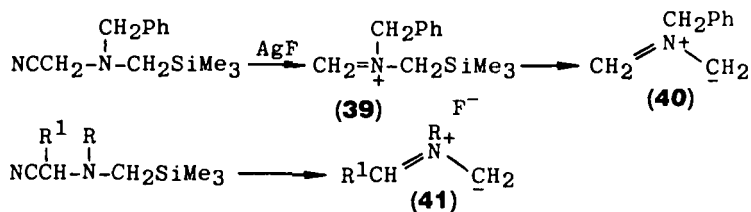


a : (*p*-methoxyphenyl)thionophosphine sulfide dimer, 100 - 110 °C in toluene
 b : MeOTf in CH_2Cl_2 c : CsF

are readily available from trimethylsilylmethyl isothiocyanate and organometallics. They are also S-methylated with methyl triflate; the resulting N-protonated iminium triflates are desilylated with fluoride ion to generate N-unsubstituted azomethine ylides **36** (86JOC1997). As ylides **36** bear a methylthio eliminating group at the ylide carbon and no N substituent, they act as synthetic equivalents of nonstabilized nitrile ylides through a cycloaddition and elimination sequence. N'-Phenyl-N-silylmethylamidines **37** are similarly N'-methylated or N'-silylated to generate N-unsubstituted azomethine ylides **38** after desilylation with cesium fluoride (85CL1411; 86JOC1997). Conjugation of the C=N bond with the phenyl moiety in the starting amidines **37** may be responsible for the regioselective N'-methylation or N'-silylation.

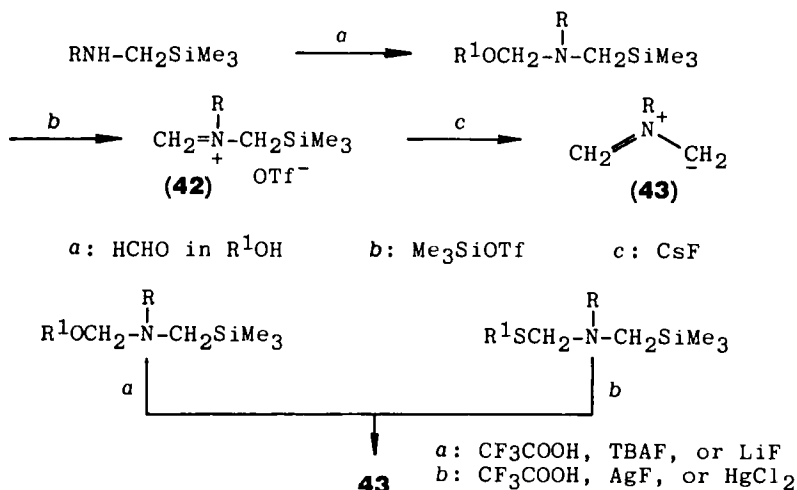


The third variation for the formation of N-silylmethyliminium salts is the removal of an α -eliminating substituent (L) from N-silylmethylamines [Eq. (4)]. The first example reported by Padwa and Chen (83TL3447) involves the silver fluoride-induced decyanation of *N*-benzyl-*N*-cyanomethyl-(trimethylsilylmethyl)amine to generate N-silylmethyliminium intermediate **39** (83TL3447). The fluoride ion attacks the silyl moiety to bring about a spontaneous desilylation to generate azomethine ylide **39**, which bears no C substituent. This method is convenient for the generation of C-unsubstituted azomethine ylides (**41**, $R^1 = H$), although the kind of α substituent R^1 is quite limited (e.g., $R^1 = Me, CN$) (84TL4917; 85JOC4006, 85T3529; 86CB813; 87JOC2427).

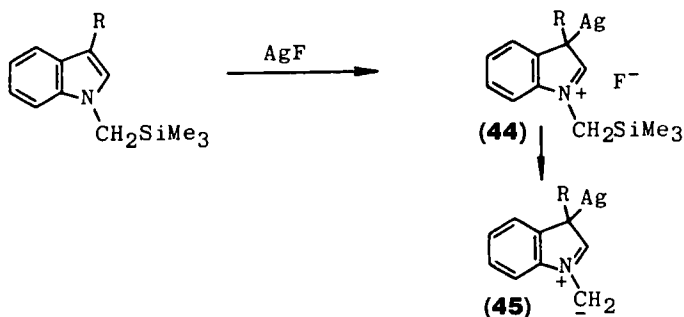


N-Alkoxymethyl(trimethylsilylmethyl)amines are convenient precursors for C-unsubstituted azomethine ylides **43** since the N-alkoxymethyl(trimethylsilylmethyl)amines are readily available by the reaction of N-alkylated silylmethylamines with formaldehyde in alcohol solvents (84CL1117). Treatment of the amines with trimethylsilyl triflate in acetonitrile or tetrahydrofuran brings about the elimination of alkoxy group R'O to form N-silylmethyliminium triflates **42**. The subsequent desilylation with cesium fluoride generates C-unsubstituted azomethine ylides **43** (84CL1117). Both steps of the alkoxy elimination and subsequent desilylation of **42** are induced by trifluoroacetic acid (85CPB896, 85CPB2762), tetrabutylammonium

fluoride (TBAF) (85CPB8896), or lithium fluoride (87JOC235). N-(Alkylthio-methyl)(trimethylsilylmethyl)amines also work as the precursors of C-unsubstituted azomethine ylides **43**. In these cases, trifluoroacetic acid (85CPB896), silver fluoride, and mercury(II) chloride (86CB813) are effective for the elimination of alkylthio group R'S and the desilylation.



Conceptually it would be possible to prepare N-silylmethyliminium salts by the addition of an electrophile to the β carbon of N-silylmethylenamines [Eq. (5)]. The reaction of 1-(trimethylsilylmethyl)indoles with silver fluoride is reported to be initiated by the addition of silver cation to the 3-position to form N-silylmethyliminium fluoride **44**, whose desilylation by fluoride ion leads to azomethine ylides **45** (86JA1104). This is the only example known for the reaction depicted by Eq. (5). The narrow application of this method may arise from the lack of a general preparation for N-silylmethylenamines.



The condensation of N-alkylated silylmethylamines with carbonyl compounds would form N-silylmethyliminium hydroxide intermediates **46**, whose desilylation leading to azomethine ylides **30** is expected to occur spontaneously. This process [Eq. (6)] is closely related to the above enamine process and looks promising. However, no such reaction has yet been reported.

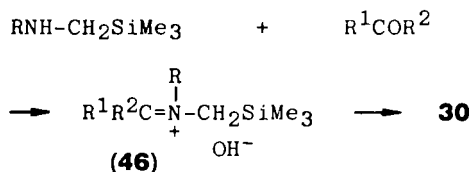
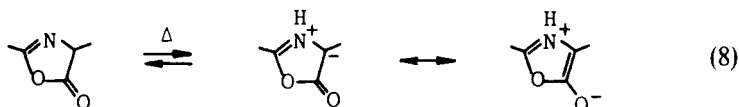
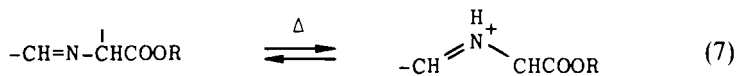


Table II summarizes the azomethine ylide 1,3-dipoles generated by the desilylation route.

C. TAUTOMERIZATION ROUTE

The hydrogen (α hydrogen) adjacent to the imine nitrogen of α -amino ester imines is highly acidic because the conjugate bases resulting from its deprotonation can be stabilized by both the imine and ester moieties. This might allow the migration of the α hydrogen to the adjacent nitrogen when the resulting species, N-protonated (or N-unsubstituted) azomethine ylide 1,3-dipoles, have a significant stability [Eq. (7)]. It is already known that 2-oxazolin-2-ones show 1,3-dipolar character as cyclic azomethine ylides through a thermal tautomerization (64AG(E)135; 70JA4340) [Eq. (8)].



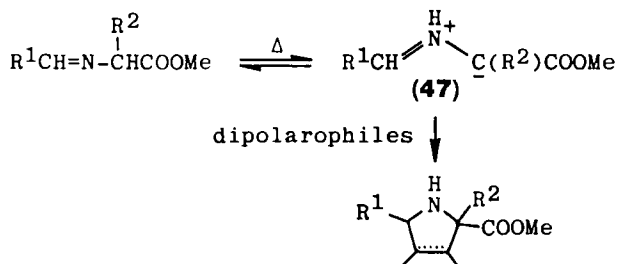
The first evidence for the existence of acyclic N-unsubstituted azomethine ylides as tautomers of imines was reported by Grigg (77CC125; 78CC109). When the imines of α -amino esters are heated in benzene or toluene in the presence of a variety of dipolarophiles, pyrrolidine- or 3-pyrroline-2-carboxylates are isolated in high yields. These heterocycles correspond to the products produced by the 1,3-dipolar cycloadditions of N-unsubstituted azomethine ylides, indicating the thermal equilibrium between the imine esters

TABLE II
AZOMETHINE YLIDES GENERATED BY THE DESILYLATION ROUTE

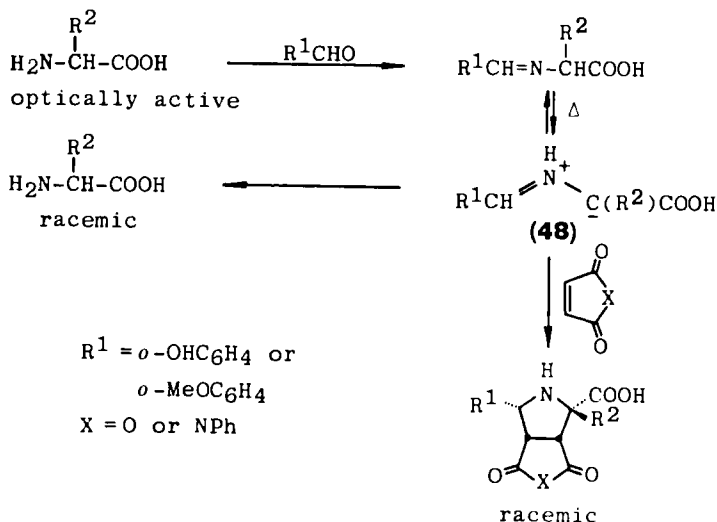
Azomethine ylides [R ¹ R ² C=NR ⁺ —C [−] R ³ R ⁴]					
R ¹	R ²	R ³	R ⁴	R	Reference
H	H	H	H	Me	84TL4917; 85JOC4006
H	H	H	H	PhCH ₂	83TL3447; 84CL1117, 84TL4917; 85JOC4006, 85T3529; 86CB813; 87JOC235
H	H	H	H	<i>c</i> -Hex	84CL1117
H	H	H	H	(<i>R</i>)-PhCH(Me)	85T3529
H	H	H	H	(<i>R</i>)-PhCH(CH ₂ OMe)	85T3529
H	H	H	H	(<i>R</i>)-PhCH(CH ₂ OMOM)	85T3529
H	H	D	D	PhCH ₂	85CPB896
<i>t</i> -Bu	H	H	H	H	86BCJ2537
Ph	H	H	H	H	82TL2589; 84CL801, 84CPB2878; 85CPB1975; 86BCJ2537
1-Naph	H	H	H	H	86BCJ2537
2-Py	H	H	H	H	86BCJ2537
Ph	Ph	H	H	H	86BCJ2537
PipCO	Ph	H	H	H	84CL2041
Ph	H	H	H	SiMe ₃	82TL2589
Me	H	H	H	PhCH ₂	85JOC4006; 87JOC235
PhCH ₂ CH ₂	H	H	H	<i>t</i> -Bu	79JA6452
	R ¹ R = (CH ₂) ₃ , R ² = R ³ = R ⁴ = H				82CPB3167
	R ¹ R = (CH ₂) ₄ , R ² = R ³ = R ⁴ = H				82CPB3167
	R ¹ R = <i>o</i> -CH ₂ C ₆ H ₄ , R ² = R ³ = R ⁴ = H				86JA1104
	R ¹ R = <i>o</i> -CH(Me)C ₆ H ₄ , R ² = R ³ = R ⁴ = H				86JA1104
	R ¹ R = <i>o</i> -CH(CHO)C ₆ H ₄ , R ² = R ³ = R ⁴ = H				86JA1104
Ph	H	H	H	Me	79JA6452
Ph	H	H	H	<i>n</i> -Bu	84CPB2878
Ph	H	H	H	PhCH ₂	84CPB2878; 87JOC235
Ph	H	H	H	EtOOCCH ₂	84CPB2878
Ph	H	H	H	MeCO	81CL1213; 83CPB3939
Ph	H	H	H	PhCO	81CL1213; 83CPB3939

Ph	H	H	H	PhCH ₂ OCO	81CL1213; 83CPB3939
2-Py	H	H	H	Me	85JOC4006
Ph(SMe)C=CH	H	H	H	PhCH ₂	83TL4303; 84JOC3314
COOMe	H	H	H	Me	85H1107
COOMe	H	H	H	PhCH ₂	85H1107
COOMe	H	H	H	MeCO	85H1107
CN	H	H	H	PhCH ₂	87JOC2427
PhCH ₂	PhCH ₂	H	H	Me	79JA6452
	R ¹ R ² = (CH ₂) ₃ C(OMe)=CH, R ³ = R ⁴ = H, R = PhCH ₂				83TL4303
	R ¹ R ² = (CH ₂) ₂ C(<i>t</i> -BuOOC)=CH, R ³ = vinyl, R ⁴ = H, R = Me				83JA6160
	R ¹ R ² = (CH ₂) ₃ C(<i>t</i> -BuOOC)=CH, R ³ = vinyl, R ⁴ = H, R = Me				83JA6160
Ph	H	H	H	OSiMe ₃	87JOC3944
Pip	H	H	H	PhCO	83CC210; 83JOC1554
SEt	H	H	H	Me	83JOC1554
SPh	H	H	H	Me	83JOC1554; 85T3559
SEt	H	H	H	<i>p</i> -NO ₂ C ₆ H ₄	83CC210, 83JOC1554
SMe	Et	H	H	H	85H2489; 86JOC1997; 87JOC2523
SMe	<i>i</i> -Pr	H	H	H	85H2489; 87JOC2523
SMe	<i>n</i> -Bu	H	H	H	86JOC1997
SPh	Me	H	H	H	85JOC4415
SMe	Ph	H	H	H	85H2489; 86JOC1997; 87JOC2523
SCOPh	Ph	H	H	H	85H2489; 87JOC2523
PhN(Me)	Me	H	H	H	85CL1411; 86JOC1997
PhN(Me)	Et	H	H	H	85CL1411; 86JOC1997
PhN(Me)	<i>n</i> -Bu	H	H	H	85CL1411; 86JOC1997
PhN(Me)	CH ₂ COOEt	H	H	H	85CL1411; 86JOC1997
PhN(Me)	Ph	H	H	H	85CL1411; 86JOC1997
OMe	Ph	H	H	Me	84JOC3314
OMe	Ph	H	H	PhCH ₂	84JOC3314
OEt	Ph	H	H	Me	83TL4303; 84JOC3314
SMe	Ph	H	H	Me	83TL4303; 84JOC3314
	R ¹ = OMe, R ² R = (CH ₂) ₃ , R ³ = R ⁴ = H				83JOC4773; 85JOC2170
	R ¹ = OMe, R ² R = CH(PhCH ₂ O)CH ₂ CH ₂ , R ³ = R ⁴ = H				80JA7993
	R ¹ = OMe, R ² R = CH(<i>o</i> -NO ₂ C ₆ H ₄ CH ₂ O)CH ₂ CH ₂ , R ³ = R ⁴ = H				85JOC2170
	R ¹ = SMe, R ² R = (CH ₂) ₃ , R ³ = R ⁴ = H				83JOC4773; 85JOC2170
	R ¹ = SMe, R ² R = (CH ₂) ₄ , R ³ = R ⁴ = H				83JOC4773

and the azomethine ylides **47**. This method of generating N-unsubstituted azomethine ylides can be called the *tautomerization route*.

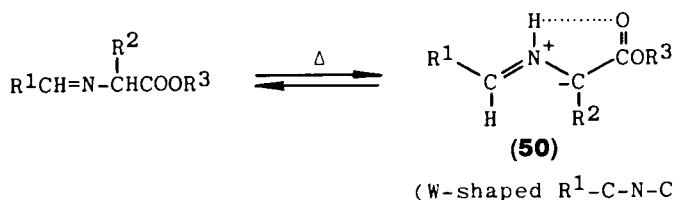
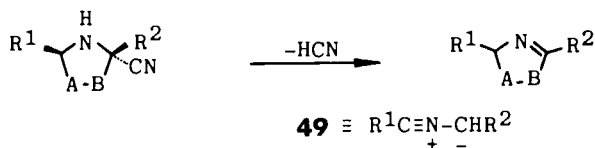
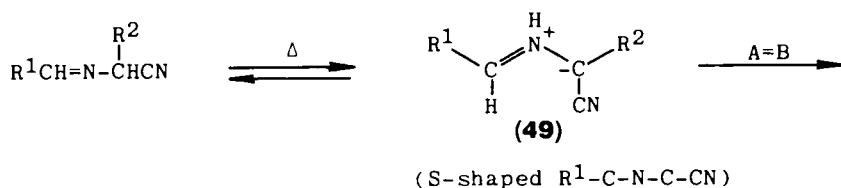


Similar azomethine ylides **48** are involved as key intermediates in the racemization of optically active α -amino acids in the presence of a catalytic amount of aldehyde (83JOC843). Grigg confirmed this mechanism (83TL4457) and carried out the reactions of optically pure α -amino acids with salicyl- or *o*-methoxybenzaldehyde and maleic anhydride or *N*-phenylmaleimide in acetic acid. Cycloadducts of N-unsubstituted azomethine ylides **48** with dipolarophiles were obtained only as racemates. These results indicate that the α -amino acids first produced the corresponding imine carboxylic acids with the retention of optical activity but these then undergo a tautomeric equilibration with N-protonated azomethine ylides **48** losing their optical purity. The ylides **48** were captured by several dipolarophiles as racemic cycloadducts. As the imines of α -amino acids usually suffer spontaneous decarboxylation (as will be discussed later in Section (II,E), the formation of



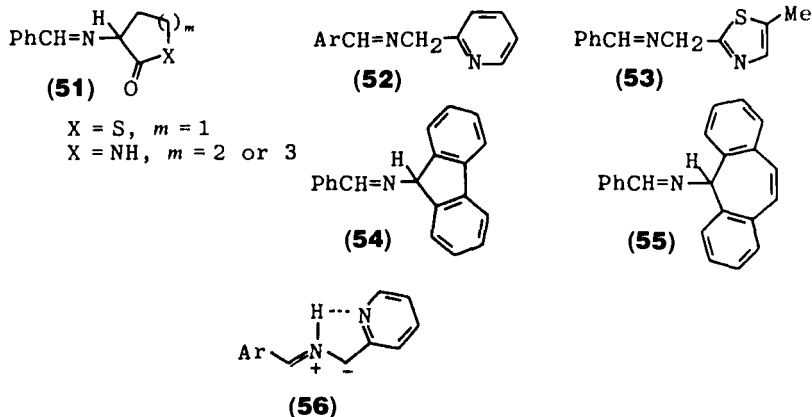
azomethine ylide carboxylic acids **48** is due to ylide stabilization by the *o*-hydroxy or *o*-methoxy substituent of R^1 .

The imines of α -amino alkanenitriles bear an anion-stabilizing cyano substituent, instead of the ester substituent of α -amino ester imines, so that the iminenitriles can also undergo a thermal equilibration with the corresponding N-unsubstituted azomethine ylides **49** (78TL2823; 82H1411; 85CL1601; 86BCJ1809). Although the cyano-stabilized azomethine ylides **49** are of course useful synthetic equivalents of the ester-stabilized azomethine ylides **50**, one difference is that cyano-stabilized ylides **49** can also be synthetic equivalents of nonstabilized nitrile ylides through a cycloaddition and HCN elimination sequence (85CL1601; 86BCJ1809). The N-unsubstituted azomethine ylides **50** of ester-stabilized types have a **W**-shaped geometry for the sequence $R^1-C-N-C-COOR^3$ as their most stable configuration. This is due to stabilization by a hydrogen bond between the ester oxygen and the NH moiety (78CC109; 83TL1201). On the other hand, the most stable geometry of cyano-stabilized ylides **49** results from a steric requirement to have an **S**-shaped geometry for the sequence $R^1-C-N-C-CN$ (86BCJ1809).



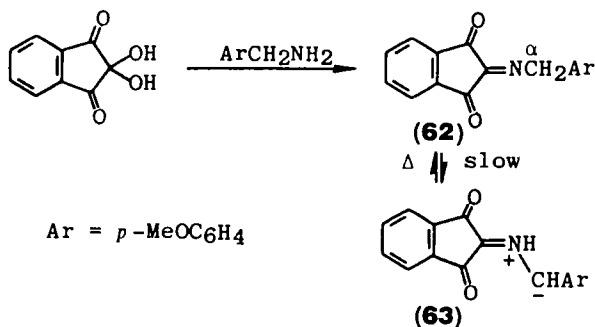
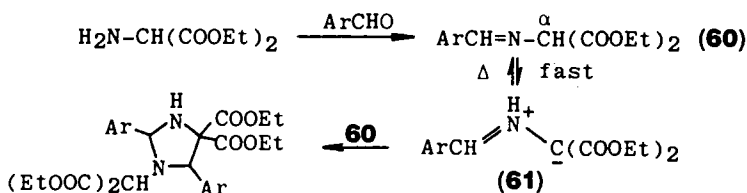
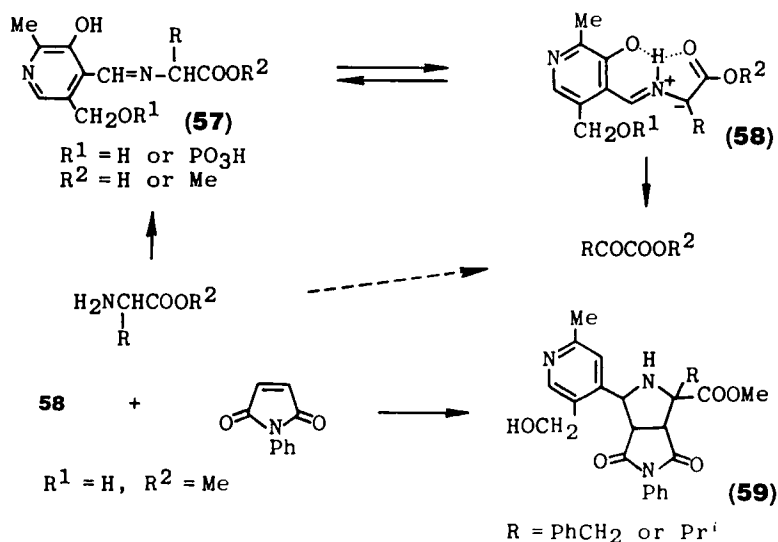
Activation of the α hydrogen of imines is not limited to ester and nitrile moieties. Thioester and amide substituents at the α carbon also serve as activating groups, as shown in the azomethine ylides derived from imines **51** (83TL4363). Surprisingly, the imines bearing 2-pyridyl (**52**), 2-thiazolyl (**53**), 2,2'-biphenylene (**54**), and 2,2'-stilbenylene (**55**) substituents are also activated enough to undergo a thermal tautomerization into the corresponding N-unsubstituted azomethine ylides. In the cases of **52** and **53**, the stabilization

of ylidic centers by a hydrogen bond between the nitrogen atom of the heterocycle and the NH proton, shown with ylide **56**, may be responsible for the high activation. Ylide stabilization by aromatization (in the case of **54**) as well as by more than three aryl substituents (in **55**) is also effective for such smooth ylide generation.



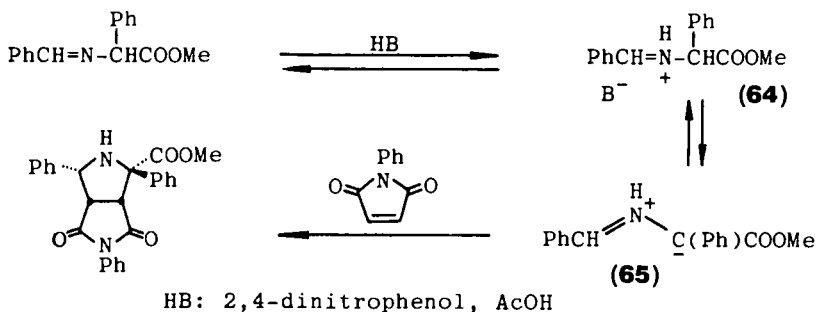
Pyridoxal or its phosphate is known to catalyze as imine forms **57** a number of enzymatic transformations of α -amino acids (e.g., transamination). It is suggested that 1,3-dipolar species **58**, tautomers of imines **57** (or their metal chelates), are involved in some pyridoxal-dependent enzymatic reactions (78TL2823). Thus, pyridoxal imines **57** react as N-unsubstituted azomethine ylide 1,3-dipoles **58** with *N*-phenylmaleimide in boiling toluene or xylene to give the cycloadducts **59**.

When the amine bearing two electron-withdrawing ester groups at the α position is condensed with aromatic aldehydes, the resulting imines **60** quickly isomerize into N-unsubstituted azomethine ylides **61**. The ylides **61** undergo cycloadditions across the $\text{C}=\text{N}$ bond of the unreacted imines **60**, giving imidazolidine cycloadducts (80TL2197). Thermolysis of the imidazolines in boiling toluene brings about their thermal retro-cycloadditions, releasing the ylides **61**, which can be captured by the added dipolarophiles. On the other hand, ninhydrin, a ketone bearing two electron-withdrawing substituents, reacts with an arylmethylamine, leading to the isolation of the corresponding imine **62**, which then can thermally equilibrate with N-unsubstituted azomethine ylide **63** (86CC602). Although both the ylides **61** and **63** carry two ylide-stabilizing α substituents on the same ylide carbon so that an identical stability is expected, the α hydrogens of the corresponding imine precursors **60** and **62** show different acidity. The imine **60**, with a more highly acidic α hydrogen, has a lower activation barrier for ylide generation. This point is important when the tautomerization route is planned in an organic synthesis.



The imine-azomethine ylide tautomerization [Eq. (7)] is catalyzed by either protonic or Lewis acids (82CC384). For example, the cycloaddition of methyl *N*-benzylidenephénylglycinate with *N*-phenylmaleimide in toluene is catalyzed by 2,4-dinitrophenol and proceeds 40 times faster than the same reaction in the absence of the catalyst. The rate-determining step of *N*-protonation of the imine forming the iminium intermediate **64** is facilitated

by the catalyst; a spontaneous deprotonation at the α position generates N-unsubstituted azomethine ylide **65**, which is trapped by the maleimide as a cycloadduct. Lewis acids are less effective than protonic acids, among which acetic acid is as efficient a catalyst as 2,4-dinitrophenol. Thus, the cycloaddition between methyl *N*-benzylidenepherylacetate and *N*-phenylmaleimide can be performed at room temperature when acetic acid (10 mol%) is employed as a catalyst in acetonitrile.

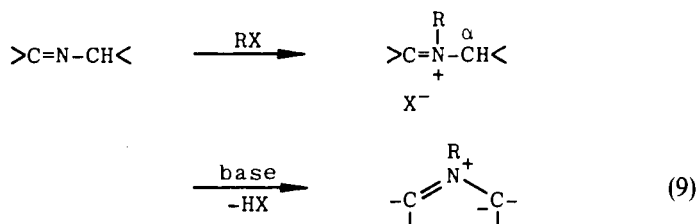


A similar rate enhancement has been observed in the cycloadditions of the imines of 2-aminoacetonitrile with olefinic dipolarophiles (85CL1601; 86BCJ1809). In these cases, strong acids, such as trifluoroacetic acid and *p*-toluenesulfonic acid, are not effective.

Table III summarizes the azomethine ylide 1,3-dipoles generated by the tautomerization route.

D. DEPROTONATION ROUTE

One of the most direct, but difficult, means of generating azomethine ylide 1,3-dipoles is a sequence of N-alkylation of imines and subsequent α -deprotonation [Eq. (9)].



This tricky sequence was first achieved by Deyrup (75JOC2048): *N*-Methylation of imines with methyl triflates produces labile *N*-methyliminium triflates **66** and **68** in quantitative yields. Deprotonation of keteneiminium triflate **66** can be best carried out with sodium bis(trimethylsilyl)amide to

TABLE III
AZOMETHINE YLIDES GENERATED BY THE TAUTOMERIZATION ROUTE

Azomethine ylides [R ¹ R ² C=NR ⁺ —C ⁻ R ³ R ⁴]					
R ¹	R ²	R ³	R ⁴	R	Reference
Ph	H	2-Py	H	H	83TL4363
<i>p</i> -Me ₂ NC ₆ H ₄	H	2-Py	H	H	83TL4363
<i>p</i> -MeOC ₆ H ₄	H	2-Py	H	H	83TL4363
<i>p</i> -CF ₃ C ₆ H ₄	H	2-Py	H	H	83TL4363
<i>p</i> -CNC ₆ H ₄	H	2-Py	H	H	83TL4363
<i>p</i> -NO ₂ C ₆ H ₄	H	2-Py	H	H	83TL4363
R ¹ = R ³ = 3-OH-5-HOCH ₂ -2-Me-4-Py, R ² = H				H	83TL4363
R ¹ R ² = 9-fluorenylidene, R ³ = Ph				H	83TL4363
R ¹ R ² = dibenzo[<i>e, f</i>]tropyliene, R ³ = Ph				H	83TL4363
R ¹ R ² = R ³ R ⁴ = 9-fluorenylidene				H	83TL4363
R ¹ R ² = 9-fluorenylidene, R ³ R ⁴ = dibenzo[<i>e, f</i>]tropyliene				H	83TL4363
COOMe	H	Ph	H	H	78TL2885; 80TL2461
COOMe	H	<i>o</i> -OHC ₆ H ₄	H	H	78TL2823
CN	H	Ph	H	H	78TL2885; 85CL1601; 86BCJ1809
CN	H	PhCO	H	H	86BCJ1809
CN	H	PhCH=CH(<i>E</i>)	H	H	86BCJ1809
CN	H	R ³ R ⁴ = (CH ₂) ₅		H	86BCJ1809
COOMe	Me	Ph	H	H	78CC109; 80TL2461; 84JCS(P1)41
COOMe	Me	<i>p</i> -Me ₂ NC ₆ H ₄	H	H	84JCS(P1)41
COOMe	Me	<i>p</i> -MeOC ₆ H ₄	H	H	80TL2461; 84JCS(P1)41
COOMe	Me	<i>p</i> -CF ₃ C ₆ H ₄	H	H	84JCS(P1)41
COOMe	<i>i</i> -Pr	Ph	H	H	78CC109
COOMe	<i>i</i> -Pr	<i>o</i> -OHC ₆ H ₄	H	H	78TL2823
COOMe	<i>i</i> -Pr	R ³ = 3-OH-5-HOCH ₂ -2-Me-4-Py, R ⁴ = R = H			78TL2823
COOMe	PhCH ₂	Ph	H	H	78CC109; 80TL2461

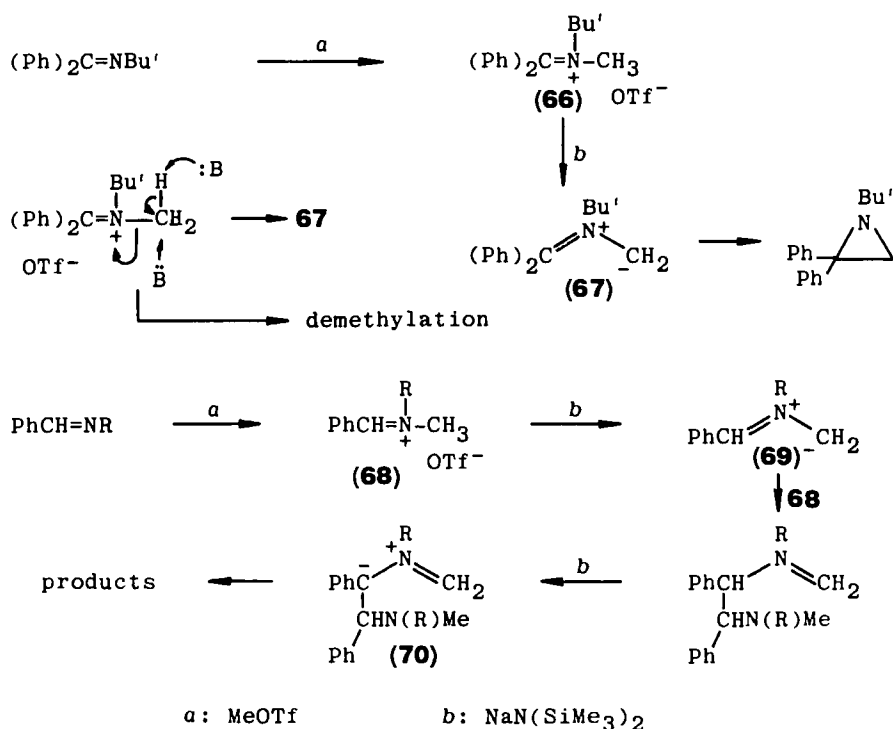
(continued)

TABLE III (Continued)

Azomethine ylides $[R^1R^2C=NR^+-C^-R^3R^4]$					
R^1	R^2	R^3	R^4	R	Reference
COOMe	PhCH ₂	<i>o</i> -OHC ₆ H ₄	H	H	78TL2823
COOMe	PhCH ₂	$R^3 = 3\text{-OH-5-HOCH}_2\text{-2-Me-4-Py}$, $R^4 = R = H$			78TL2823
COOMe	3-InCH ₂	Ph	H	H	78CC109
COOMe	PhCH ₂ SCH ₂	Ph	H	H	78CC109
COOMe	1- <i>c</i> -pentenyl	2-Naph	H	H	83TL1201
COOMe	Ph	4-Pentenyl	H	H	85T3547
COOMe	Ph	5-Hexenyl	H	H	85T3547
COOMe	Ph	$R^3 = 1,1\text{-dimethyl-3-butenyl}$, $R^4 = R = H$			85T3547
COOMe	Ph	PhCH=CH(<i>E</i>)	H	H	83TL1201
COOMe	Ph	Ph	H	H	77CC125; 78CC109; 80TL2461; 82CC384; 84JCS(P1)41
COOMe	Ph	<i>p</i> -Me ₂ NC ₆ H ₄	H	H	84JCS(P1)41
COOMe	Ph	<i>p</i> -MeC ₆ H ₄	H	H	80TL2461
COOMe	Ph	<i>p</i> -MeOC ₆ H ₄	H	H	77CC125; 78CC109; 80TL2461; 83TL4457; 84JCS(P1)41
COOMe	Ph	<i>o</i> -MeOC ₆ H ₄	H	H	83TL4457
COOMe	Ph	<i>p</i> -CF ₃ C ₆ H ₄	H	H	84JCS(P1)41
COOMe	Ph	<i>p</i> -CNC ₆ H ₄	H	H	82CC384; 84JCS(P1)41
COOMe	Ph	<i>p</i> -NO ₂ C ₆ H ₄	H	H	77CC125; 80TL2461; 82CC384; 84JCS(P1)41
COOMe	Ph	<i>o</i> -allyloxy-C ₆ H ₄	H	H	85T3547
	$R^1 = \text{COOMe}$, $R^2 = \text{Ph}$, $R^3 = o\text{-(2-Me-2-pentenylloxy)-C}_6\text{H}_4$, $R^4 = R = H$				85T3547
COOMe	Ph	2-Furyl	H	H	77CC125
COOMe	Ph	2-Thienyl	H	H	78CC109
COOMe	Ph	3-Py	H	H	77CC125
CN	Ph	Et	H	H	86BCJ1809

CN	Ph	3-c-hexenyl	H	H	86BCJ1809
CN	Ph	MeCH=CH(E)	H	H	86BCJ1809
CN	Ph	PhCH=CH(E)	H	H	86BCJ1809
CN	Ph	PhCH=CMe(E)	H	H	86BCJ1809
CN	Ph	Ph	H	H	82H1411; 86BCJ1809
CN	Ph	PhCO	H	H	86BCJ1809
CN	Ph	Me	Me	H	86BCJ1809
CN	Ph	Me	Et	H	86BCJ1809
CN	Ph	$R^3R^4 = (CH_2)_4$		H	86BCJ1809
CN	Ph	$R^3R^4 = (CH_2)_5$		H	86BCJ1809
	$R^1R^2 = COS(CH_2)_2$	Ph	H	H	83TL4363
	$R^1R^2 = CONH(CH_2)_2$	Ph	H	H	83TL4363
	$R^1R^2 = CONH(CH_2)_3$	Ph	H	H	83TL4363
	$R^1R^2 = o-CONHC_6H_4$	Ph	H	H	86CC602
COOH	PhCH ₂	<i>o</i> -OHC ₆ H ₄	H	H	83TL4457
COOH	PhCH ₂	<i>o</i> -MeOC ₆ H ₄	H	H	83TL4457
COOH	MeS(CH ₂) ₂	<i>o</i> -OHC ₆ H ₄	H	H	83TL4457
COOH	H ₂ N(CH ₂) ₄	<i>o</i> -OHC ₆ H ₄	H	H	83TL4457
COOH	<i>i</i> -PrCH ₂	<i>o</i> -OHC ₆ H ₄	H	H	83TL4457
COOH	HOCH ₂	<i>o</i> -OHC ₆ H ₄	H	H	83TL4457
COOEt	COOEt	Ph	H	H	80TL2197
COOEt	COOEt	<i>p</i> -CF ₃ C ₆ H ₄	H	H	80TL2197
COOEt	COOEt	<i>p</i> -NO ₂ C ₆ H ₄	H	H	80TL2197
COOEt	COOEt	2-Furyl	H	H	80TL2197
COOEt	COOEt	2-Thienyl	H	H	80TL2197
COOEt	COOEt	2-Py	H	H	80TL2197
COOEt	COOEt	$R^3 = 5-(2-Ph-thiazolyl), R^4 = R = H$			80TL2197
	$R^1R^2 = o-COC_6H_4CO$	<i>p</i> -MeOC ₆ H ₄	H	H	86CC602
	$R^1R^2 = o-COC_6H_4CO$	COOMe	H	H	86CC421
	$R^1R^2 = R^3R^4 = o-COC_6H_4CO$			H	86CC421

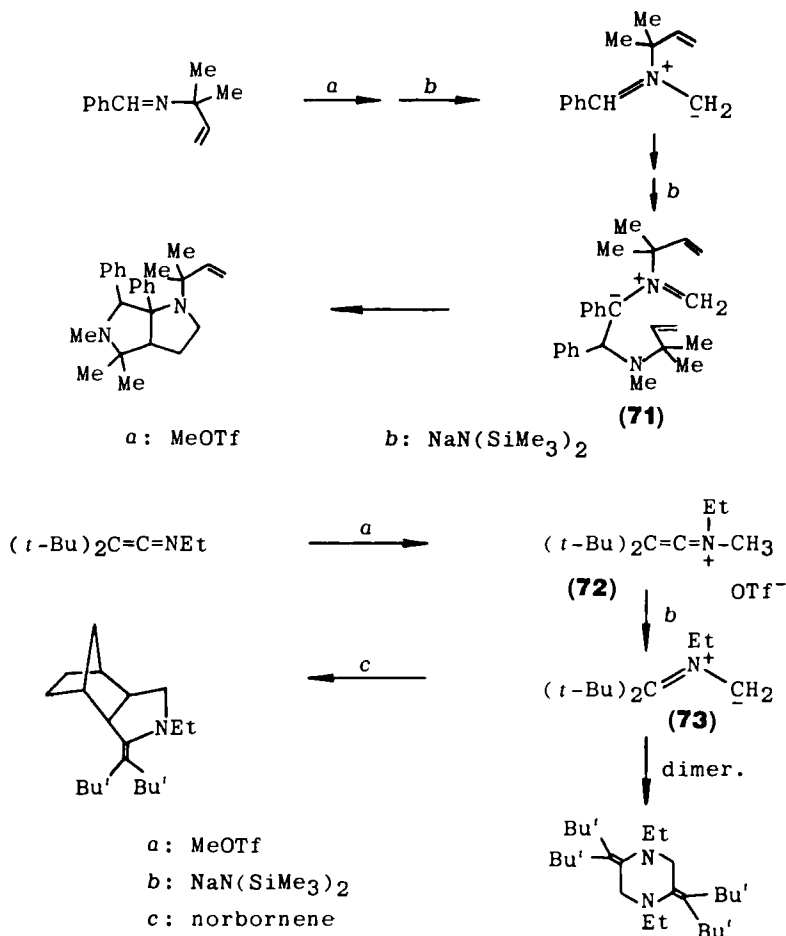
generate azomethine ylide **67**, which is captured as a cyclized isomer, 1-*t*-butyl-2,2-diphenylaziridine. However, the deprotonation is accompanied by a demethylation providing the starting imine even when a nonnucleophilic strong base is used. On the other hand, deprotonation of aldiminium triflate **68** gives a number of dimeric products arising from the substituted azomethine ylide **70**, which is itself derived from a nucleophilic addition of the resulting azomethine ylide **69** to the iminium salt **68** and subsequent deprotonation.



When the above reaction sequence is applied to an *N*-allylaldimine, the substituted azomethine ylide **71**, a transient intermediate, can be trapped intramolecularly to give a bicyclic cycloadduct (77TL3437).

A similar treatment of stable keteneiminium triflate **72** with sodium bis(trimethylsilyl)amide generates azomethine ylide **73**, together with a small amount of the demethylated product of **72**. Ylide **73** undergoes readily dimerizes, leading to 1,4-diethyl-2,5-bis[2,2-dimethyl-1-(*t*-butyl)propyridene]-piperazine when no dipolarophile is present. The trapping of ylide **73** with electron-deficient olefins is completely unsuccessful because these activated olefins cannot withstand such strongly basic conditions. The only dipolar-

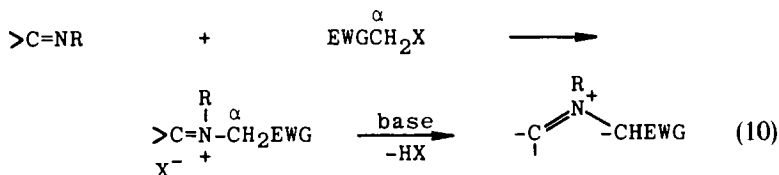
ophile successful in trapping **73** is norbornene, which affords a quantitative yield of the 1:1 cycloadduct (78JOC501).



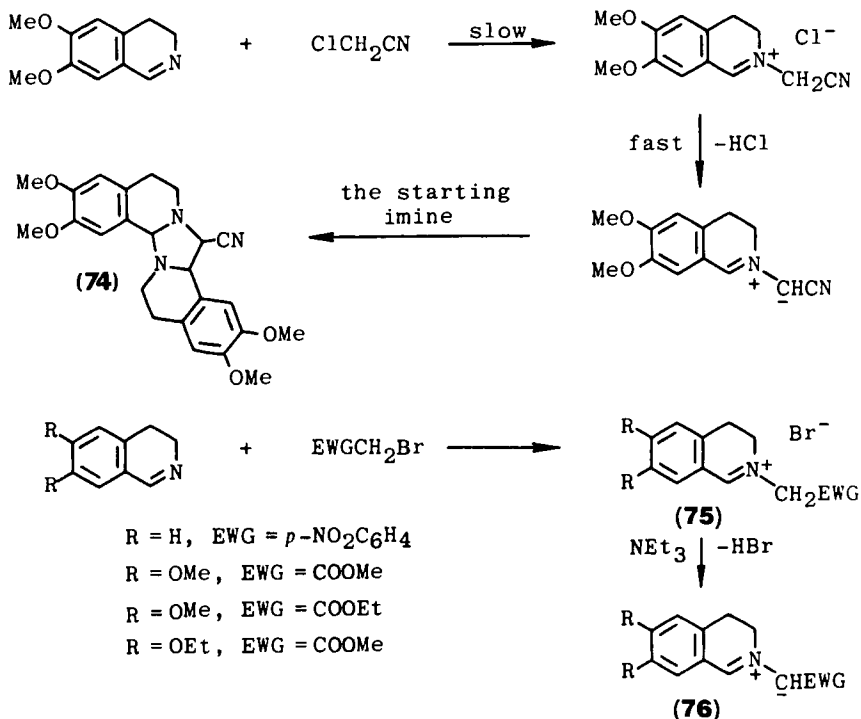
Although the N-alkylation and deprotonation sequence pioneered by Deyrup may be referred to as the *deprotonation route*, it has to be concluded on the basis of the above results that this sequence itself [Eq. (9)] cannot be a general route to azomethine ylides. Some modification is needed.

If the acidity of the α hydrogen of iminium intermediates is increased, the α -deprotonation will be smoothly carried out by the aid of a weak base avoiding the undesired dealkylation. For this purpose, an electron-withdrawing substituent (EWG) is required on the α carbon of iminium salts; N-alkylation of imines with the alkyl halides bearing an α -electron-withdrawing group

looks promising since these halides are generally reactive alkylating agents [Eq. (10)].



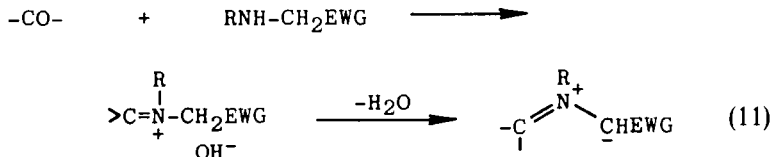
If anion stabilization by an EWG is too strong, the resulting iminium salts quickly lose the α hydrogen, under the alkylation conditions, to lead to a spontaneous generation of the corresponding azomethine ylides, which undergo a ready cycloaddition to the starting imines. The reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline with chloroacetonitrile giving cycloadduct **74** is such a case (82LA924). Alkylating agents carrying an appropriate EWG such as *p*-nitrobenzyl bromide (63TL1441) and α -bromoacetates (82LA2146; 83JCS(P1)1961, 83T369) have been successfully employed in the preparation of iminium precursors **75**. So far, several derivatives of 3,4-



dihydroisoquinoline are the only imines ever employed in the azomethine ylide generation according to Eq. (10). Iminium salts **75** liberate azomethine ylides **76** on treatment with triethylamine as a weak base.

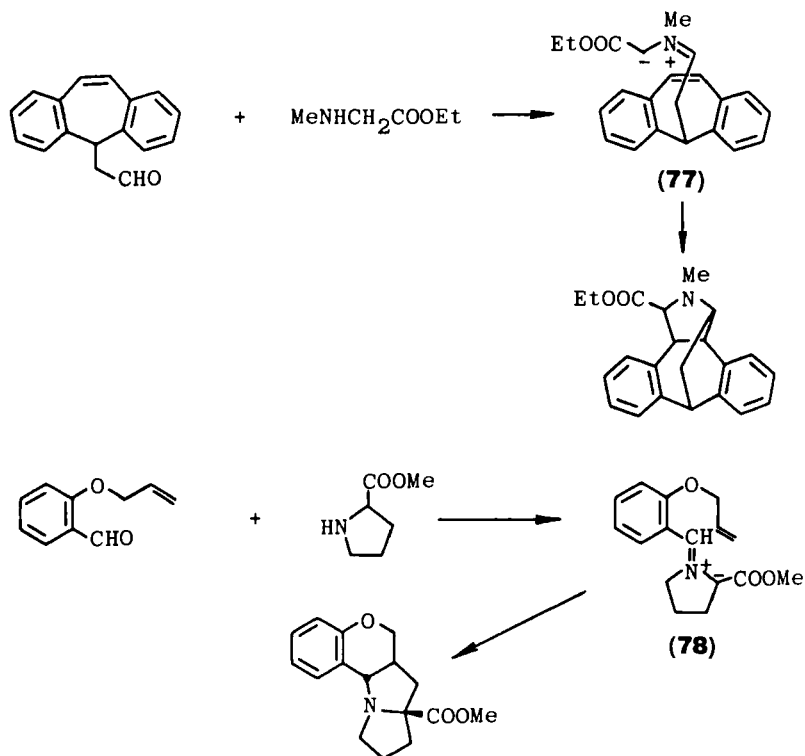
In summary, this modified sequence [Eq. (10)] finds only very limited application in organic synthesis. The difficulty encountered in Eq. (10) would be solved by a quick N-alkylation of imines with highly reactive alkylating agents (e.g., EWG-CH₂X, X = OTf). However, such powerful alkylating reagents are not available at present. Another solution would be a quick N-alkylation of the imines bearing an α -EWG with a highly reactive agent such as methyl triflate. This method will surely work well. However, this is virtually identical with the aforementioned tautomerization route (Section II,C), so that little synthetic advantage will result.

Probably the most useful modification for the deprotonation route will be the condensation of N-substituted α -amino esters or derivatives (EWG = COOR, CN, etc.) with carbonyl compounds [Eq. (11)]. The intermediate iminium salts bear a highly basic hydroxide ion as a counteranion, which deprotonates the α hydrogen immediately after its formation. The EWG-stabilized azomethine ylides thus generated will be smoothly trapped by the added dipolarophiles since they find no other reactive reagents in the reaction mixture.

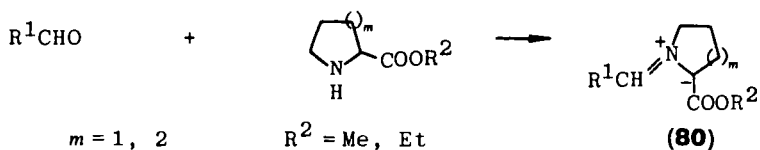
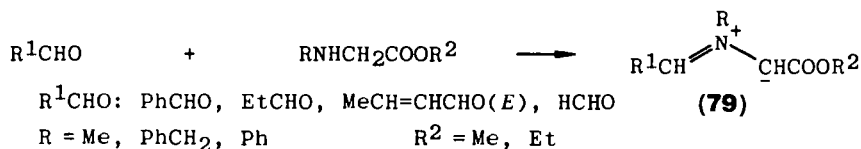


According to Eq. (11), Confalone has presented a new method of generation of azomethine ylides through the condensation of N-substituted α -amino esters with aldehydes (83JOC2994; 84JA7175). Thus, 5-formylmethyldibenzo-[*a,d*]tropyliene or *o*-(allyloxy)benzaldehyde is heated with ethyl sarcosinate or methyl prolinates under reflux in toluene. The water formed is continuously driven off with the aid of a Dean-Stark trap. The ester-stabilized azomethine ylide **77** or **78** quantitatively generated is trapped in an intramolecular fashion.

A little later it was demonstrated that the azomethine ylides generated by the condensation method [Eq. (11)] can be successfully applied to the intermolecular cycloadditions with a wide variety of dipolarophiles. Aromatic aldehydes, aliphatic aldehydes (but not acetaldehyde), α,β -unsaturated aldehydes, and formaldehyde can be employed as the carbonyl components; α -amino esters bearing an N substituent (N-alkyl or N-aryl glycines) and ones bearing an N substituent and an α substituent (prolinates and pipercolinates) are used (85TL2775; 86CL973, 86CL1271; 87BCJ4067). A number of ester-stabilized azomethine ylides **79** and **80** bearing the corresponding N and C

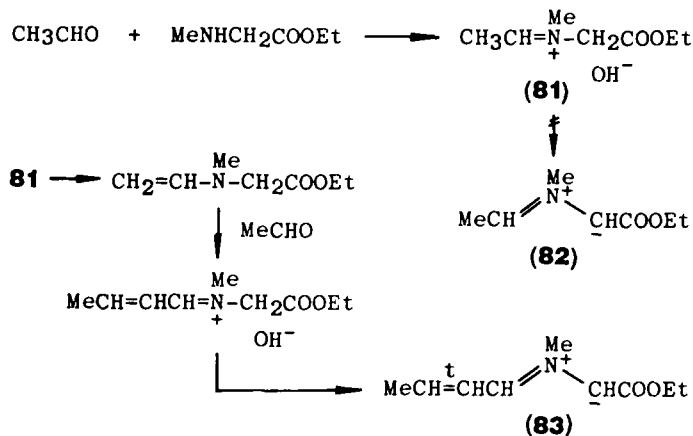


substituents become accessible by this method. The procedure is very simple: A mixture of carbonyl compound and α -amino ester is heated in the presence of a dipolarophile under reflux in toluene with a continuous removal of water with a Dean-Stark trap. Intermolecular trapping of the azomethine ylides **79** and **80** is achieved without any difficulty to give good yields of cycloadducts.

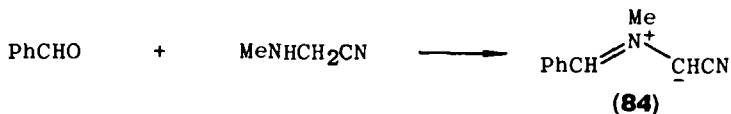


In the reaction of acetaldehyde with ethyl sarcosinate, the initial condensate **81** quickly loses an ω hydrogen to generate an enamine interme-

diate rather than the α -deprotonation leading to C-methyl-substituted azomethine ylide **82**. The subsequent addition of another molecule of acetaldehyde to the enamine intermediate provides, after a spontaneous dehydration, C-(1-propenyl)-substituted azomethine ylide **83** in good yield (86CL1271; 87BCJ4067).

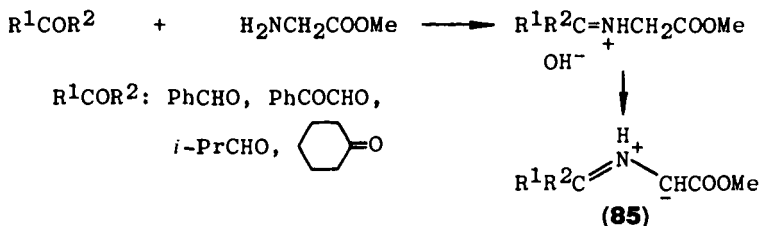


Use of N-substituted 2-aminonitriles in the condensation with carbonyl compounds generates cyano-stabilized azomethine ylides (87BCJ4067). The reaction of benzaldehyde with (methylamino)acetonitrile leading to ylide **84** is an example.

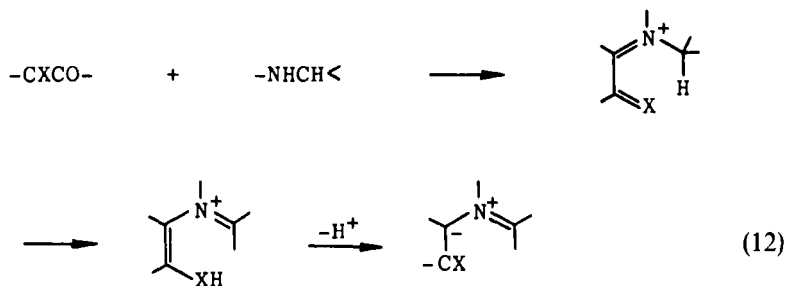


In the process shown in Eq. (11), N-unsubstituted α -amino esters are employed instead of N-substituted derivatives. The reaction of methyl glycinate with carbonyl compounds produces iminium hydroxide intermediates, which are then dehydrated generating N-unsubstituted azomethine ylides **85** (86CL1271; 87BCJ4067). Therefore, this method is closely related to the tautomerization route, especially to the acid-catalyzed tautomerization (Section II,C). Benzaldehyde, phenylglyoxal, 2-methylpropanal, and cyclohexanone can be used as carbonyl compounds; the corresponding azomethine ylides are trapped with *N*-methylmaleimide in excellent yields.

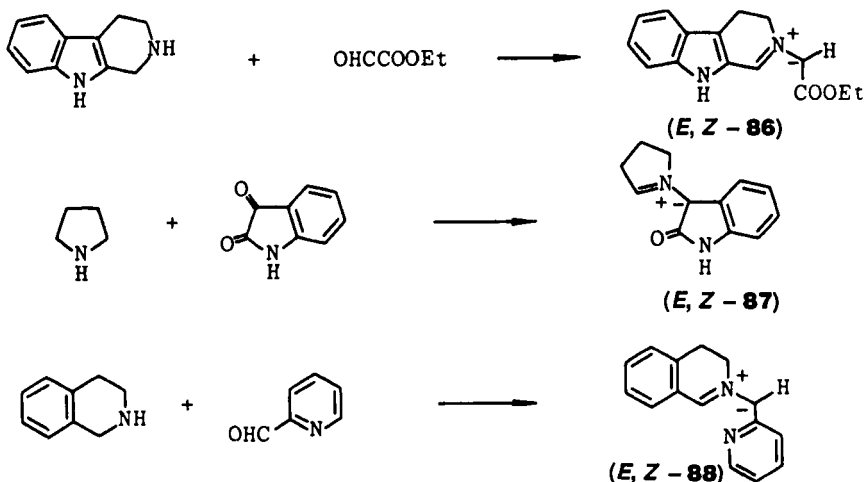
Even if the α hydrogen of an amine is not highly acidic, its activation is possible by condensation with a special type of carbonyl compound. Grigg's idea (86CC602) is given in Eq. (12), in which carbonyl compounds bearing a conjugated $\text{C}=\text{X}$ moiety ($\text{X} = \text{heteroatom}$) are condensed with secondary



amines. The intermediate iminium salts undergo a 1,5-proton migration to functionalize, or activate, the inactive α position of amines. Subsequent deprotonation generates azomethine ylides. According to the sequence shown in Eq. (12), azomethine ylide generation should occur stereoselectively.

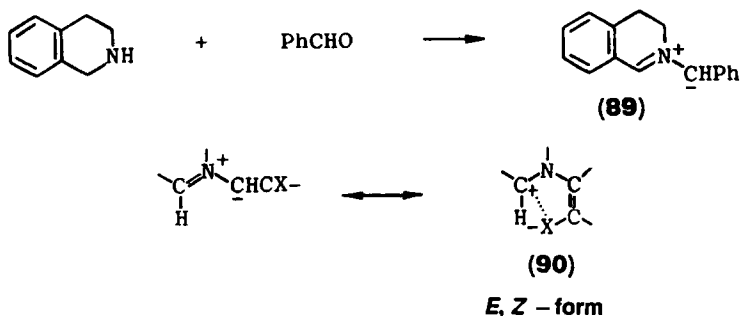


1,2,3,4-Tetrahydro- β -carboline reacts with ethyl glyoxylate in acetonitrile generating azomethine ylide (*E,Z*)-**86**. Even the extremely inert α hydrogen of pyrrolidine can be activated in the condensation with isatin leading to ylide (*E,Z*)-**87** (86CC602). It is surprising that pyridine-2-carbaldehyde also serves

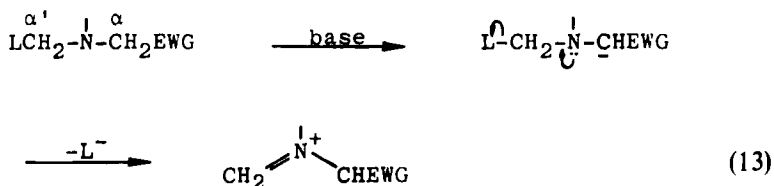


as an imine-activating carbonyl compound and succeeds in the generation of azomethine ylide (*E,Z*)-**88** by condensing with 1,2,3,4-tetrahydroisoquinoline. All these azomethine ylides (**86–88**) have been trapped as cycloadducts with *N*-methylmaleimide in high yields. Stereostructures of these maleimide cycloadducts reflect the configurations of reacting ylides **86–88**, which are found to be stereochemically pure and in accord with the 1,5-proton migration mechanism shown in Eq. (12).

Though nonstereoselective, even benzaldehyde generates azomethine ylide **89** in the condensation with 1,2,3,4-tetrahydroisoquinoline (86CC602). This result indicates that ylides **86–88**, derived from the conjugated carbonyl compounds, may have been generated through a pathway other than the 1,5-proton migration mechanism [Eq. (12)]. The observed high stereoselectivity does not necessarily reflect the kinetically controlled ylide generation. A similar stereoselective cycloaddition of the *E* and *Z* forms of carbonyl-stabilized azomethine ylides has been observed and explained on the grounds of thermodynamic stability of the extended 1,5-dipoles **90** (86CL1271; 87BCJ4067). Ylide **89** must have arisen from the intermediate iminium hydroxide by simple deprotonation. Accordingly, the modified deprotonation route [Eq. (11)] must be further extended in the future to a wide variety of secondary amines (e.g., RNHCH_2EWG , $\text{EWG} = \text{Ar}$, $\text{RCH}=\text{CH}$, $\text{HC}\equiv\text{C}$, $\text{PO}(\text{OR}')_2$).

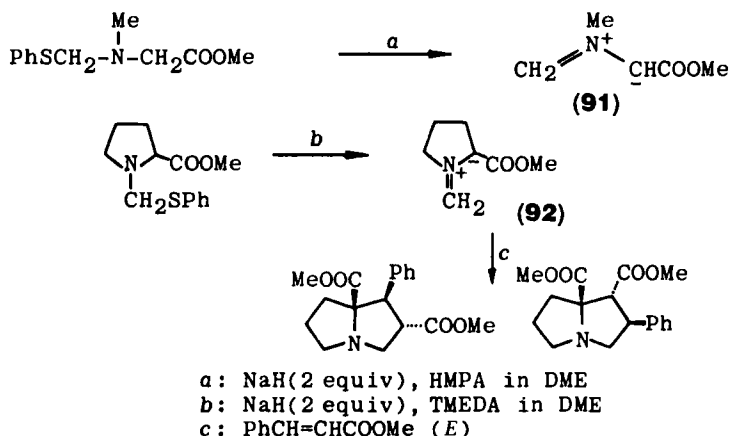


Equation (13) shows one variation of the deprotonation route in which the amines bearing an α -electron-withdrawing (EWG) and an α' -eliminating (L) group are first α -deprotonated with base. The resulting anionic species lose the eliminating group to generate EWG-stabilized azomethine ylides. This

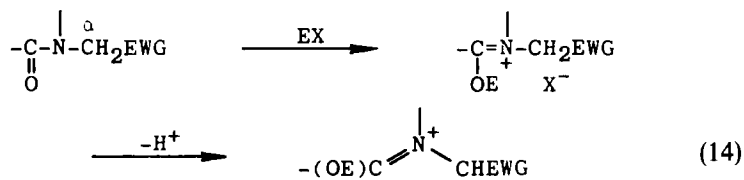


variation is closely related with the modified version [Eq. (4) in Section II,B] of the aforementioned desilylation route.

The only example has been reported by Achiwa (84TL1579). Thus, methyl *N*-(phenylthiomethyl)sarcosinate is treated with sodium hydride (2 equivalents) in 1,2-dimethoxyethane (DME) and hexamethylphosphoric triamide (HMPA) to lead to azomethine ylide **91**. A cyclic ylide, **92**, is generated by a similar procedure using methyl *N*-(phenylthiomethyl)prolinate and trapped with a dipolarophile to give the corresponding cycloadduct as a 1:1 regioisomeric mixture.

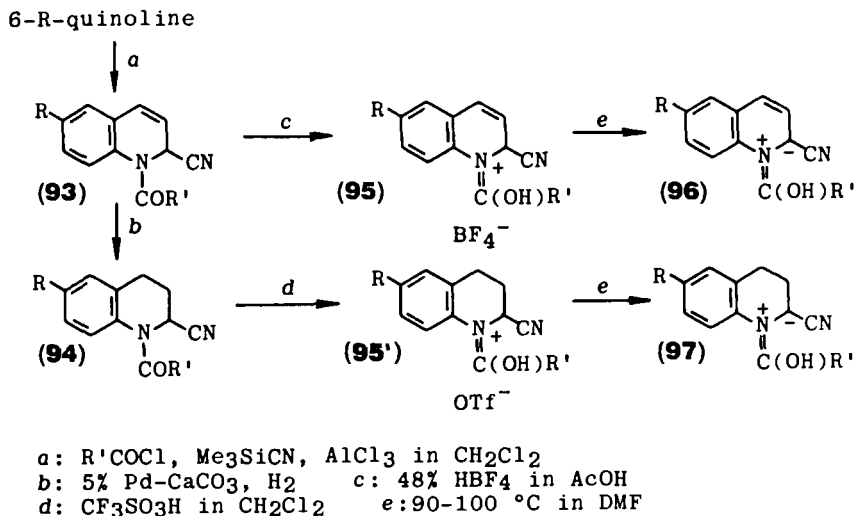


Amides derived from secondary amines bearing an electron-withdrawing group at a α -position will be alkylated or protonated on the amide oxygen to produce iminium salts [Eq. (14)]. Elimination of the acidic α hydrogen leads to azomethine ylides. A similar sequence has already been applied with great success to the modified desilylation route [Eq. (3), Section II,B].



1,2-Dihydro- (**93**) and 1,2,3,4-tetrahydroquinoline Reissert compounds (**94**) can be the azomethine ylide precursors for the above purpose; **93** is readily available from quinolines, acyl chlorides, trimethylsilyl cyanide, and aluminum chloride, and **94** by catalytic hydrogenation of **93**. These Reissert compounds are first O-protonated with HBF_4 in acetic acid or $\text{CF}_3\text{SO}_3\text{H}$ in dichloromethane and the resulting salts, **95** and **95'**, are then heated

in dimethylformamide (DMF) generating azomethine ylides **96** and **97** (85JOC722). No further extension of this facile process is known so far.



Azomethine ylide 1,3-dipoles generated through the deprotonation route are listed in Table IV.

E. DECARBOXYLATION ROUTE

During investigations on the carbonyl-assisted decarboxylation of N-alkylated α -amino acids, Rizzi found that azomethine ylide intermediates are involved in the decarboxylative condensation (70JOC2069). Heating sarcosine and benzophenone at $170^\circ C$ (or benzaldehyde at $150-170^\circ C$) gave 3-methyl-2,2,5,5-tetraphenyloxazolidine, which corresponds to the cycloadduct of azomethine ylide **98** to the carbonyl compound. This sequence may involve the initial formation of iminium carboxylate betaines and subsequent decarboxylation to generate nonstabilized azomethine ylides [Eq. (15)]. This

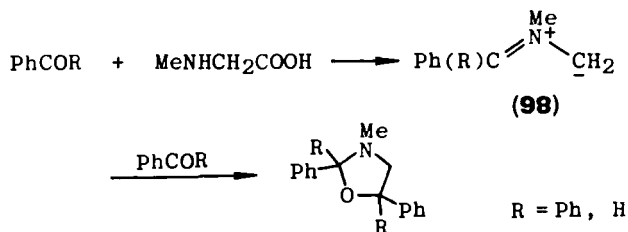
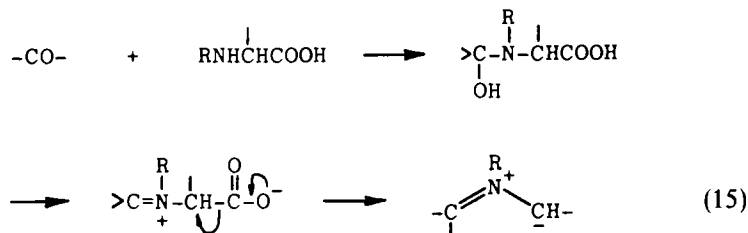


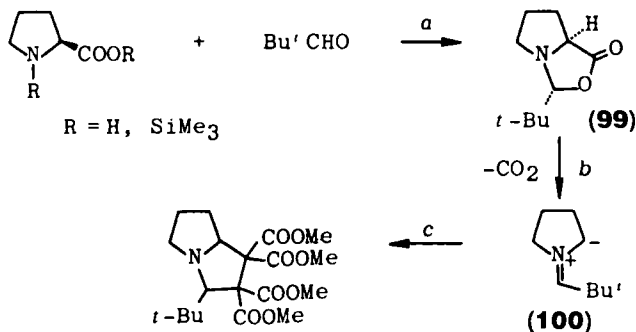
TABLE IV
AZOMETHINE YLIDES GENERATED BY THE DEPROTONATION ROUTE

Azomethine ylides [$R^1R^2C=NR^+-C^-R^3R^4$]					
R^1	R^2	R^3	R^4	R	Reference
Ph	H	$RR^3 = o-(CH_2)_2C_6H_4$	H		86CC602
2-Py	H	$RR^3 = o-(CH_2)_2C_6H_4$	H		86CC602
2-Py	H	$RR^3 = 3-(CH_2)_2-2-In$	H		86CC602
$R^1R^2 = (t-Bu)_2C=C$, $R^3 = H$			H	Et	78JOC501
Ph	Ph	H	H	<i>t</i> -Bu	75JOC2048
COOMe	H	<i>i</i> -Pr	H	H	86CL1271; 87BCJ4067
COOMe	H	Ph	H	H	86CL1271; 87BCJ4067
COOMe	H	PhCO	H	H	86CL1271; 87BCJ4067
COOMe	H	$R^3R^4 = (CH_2)_5$		H	86CL1271; 87BCJ4067
COOMe	H	H	H	Me	84TL1579
COOMe	H	H	H	Ph	86CL973; 87BCJ4067
COOMe	H	Et	H	Ph	86CL1271; 87BCJ4067
COOMe	H	Ph	H	$PhCH_2$	85TL2775
COOMe	H	Ph	H	Ph	86CL1271; 87BCJ4067
COOMe	H	<i>p</i> -MeOC ₆ H ₄	H	Me	82LA2146
COOMe	H	$R^3R = 2-(CH_2)_2-4,5-di-MeO-C_6H_2$, $R^4 = H$			82LA2146; 83JCS(P1)1961; 83T369
COOMe	H	$R^3R = 2-(CH_2)_2-4,5-di-EtO-C_6H_2$, $R^4 = H$			83T369
COOEt	H	H	H	Me	86CL973; 87BCJ4067
COOEt	H	Et	H	Me	86CL1271; 87BCJ4067
COOEt	H	$MeCH=CH(E)$	H	Me	86CL1271; 87BCJ4067
COOEt	H	Ph	H	Me	86CL1271; 87BCJ4067
COOEt	H	$RR^3 = 3-(CH_2)_2-2-In$	H		86CC602
COOEt	H	$R^3R = 2-(CH_2)_2-4,5-di-MeO-C_6H_2$, $R^4 = H$			82LA924, 82LA2146; 83T369
CN	H	Ph	H	Me	87BCJ4067
CN	H	$R^3R = 2-(CH_2)_2-4,5-di-MeO-C_6H_2$, $R^4 = H$			82LA924; 83T369
COPh	H	$RR^3 = o-(CH_2)_2C_6H_4$, $R^4 = H$			86CC602
COOMe		$R^2R = (CH_2)_3$, $R^3 = R^4 = H$			84TL1579
COOMe		$R^2R = (CH_2)_4$, $R^3 = R^4 = H$			84TL1579
COOMe		$R^2R = (CH_2)_3$, $R^3 = Ph$, $R^4 = H$			85TL2775
COOEt		$R^2R = (CH_2)_4$, $R^3 = Ph$, $R^4 = H$			85TL2775
CN		$R^2R = o-(CH_2)_2C_6H_4$, $R^3 = OH$, $R^4 = Me$			85JOC722
CN		$R^2R = 2-(CH_2)_2-4-MeOC_6H_4$, $R^3 = OH$, $R^4 = Me$			85JOC722
CN		$R^2R = 2-(CH_2)_2-4-MeOC_6H_4$, $R^3 = OH$, $R^4 = Ph$			85JOC722
$R^1R^2 = o-CONHC_6H_4$, $R^3R = (CH_2)_3$, $R^4 = H$					86CC602



example offers the first generation of azomethine ylides from α -amino acids and carbonyl compounds through the *decarboxylation route*.

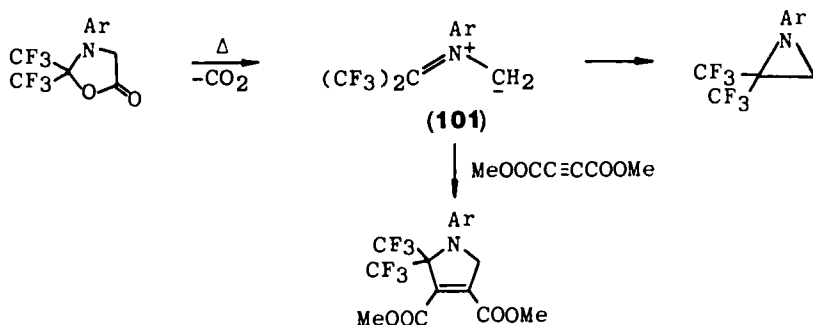
One important fact has emerged regarding the mechanism of the decarboxylative ylide generation from α -amino acids and carbonyl compounds: A water-sensitive and thermally labile bicyclic lactone **99** can be isolated as a single stereoisomer from the reaction of proline or its O,N-disilyl derivative with pivalaldehyde below 40°C (83JA5390). On heating under reflux in toluene **99** loses carbon dioxide through a reversal of a cycloaddition reaction to generate azomethine ylide **100**. Ylide **100** can be captured in the cycloaddition using tetramethyl ethenetetracarboxylate, but no attention has been paid to the stereochemistry of the cycloadduct (76CSR377).



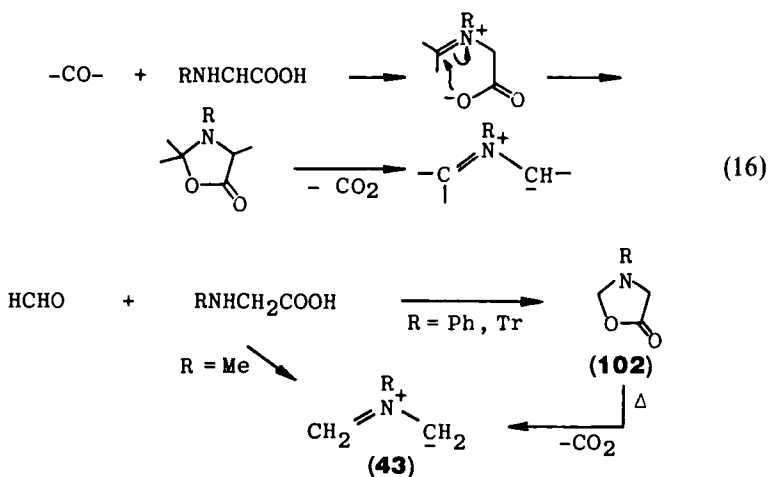
a: below 40 °C in hexane or CCl₄, Dean-Stark trap
 b: reflux in toluene c: (MeOOC)₂C=C(COOMe)₂

Though a higher reaction temperature is needed (185–195°C), 3-aryl-2,2-bis(trifluoromethyl)-5-oxazolidinones also undergo a cycloreversion losing carbon dioxide (77MI1). The azomethine ylides **101**, substituted with two trifluoromethyl moieties on the same carbon, either cyclize into the corresponding aziridines when no dipolarophile is present, or are captured by dimethyl acetylenedicarboxylate as cycloadducts.

These two examples of thermolysis of 5-oxazolidinone derivatives indicate that cyclic intermediates, 5-oxazolidinones, are most likely involved in the decarboxylative condensation of N-substituted α -amino acids with carbonyl

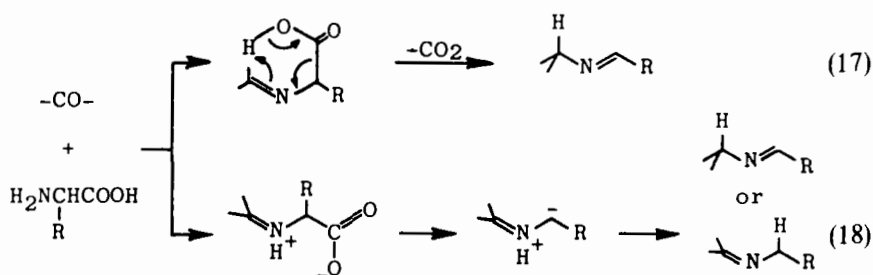


compounds. Thus, Rizzi's mechanism, shown in Eq. (15) is to be partly revised as Eq. (16). The iminium carboxylates as the initial condensates cyclize into thermally labile 5-oxazolidinone intermediates and they undergo a ready thermal decarboxylation leading to azomethine ylides. The intermediacy of 5-oxazolidinones is further supported by the following results. In the condensation of N-substituted glycines with paraformaldehyde, a small N substituent, such as a methyl moiety, results in direct ylide generation. The corresponding 5-oxazolidinones **102** are isolable when the N substituent is bulky like phenyl or trityl. These oxazolidinones lose carbon dioxide when heated under reflux in toluene generating C-unsubstituted azomethine ylides **43** (86CL973; 87BCJ4079).

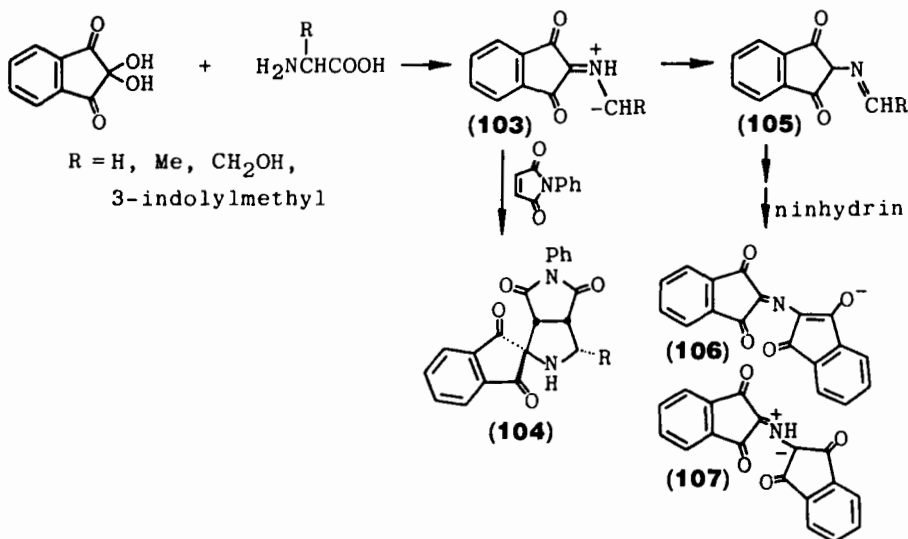


The carbonyl-assisted decarboxylation of α -amino acids is closely related to an important reaction: a decarboxylative transamination of N-unsubstituted α -amino acids. It has been widely accepted that this decarboxylative transamination proceeds through the initial formation of imine carboxylic

acid intermediates and subsequent 1,5-hydrogen shift in a concerted manner [Eq. (17)]. Based on the ylide-trapping experiment shown below, it is quite certain that the concerted mechanism has to be replaced by an alternative [Eq. (18)], which involves the initial formation of iminium carboxylate intermediates, followed by a decarboxylation generating N-unsubstituted azomethine ylide intermediates. A 1,2-proton migration by an azomethine ylide-imine tautomerism leads to two regioisomeric imines.

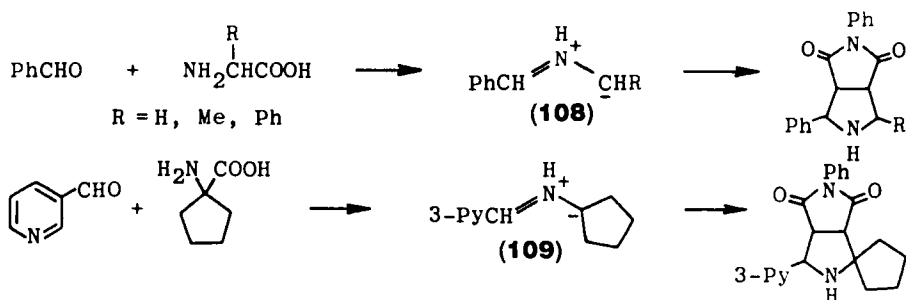


Ninhydrin is allowed to react with α -amino acids in methanol at room temperature in the presence of *N*-phenylmaleimide to give stereoselective cycloadducts **104** in good yields, confirming the ylide intermediacy (84CC180). The N-unsubstituted azomethine ylide intermediates **103**, when no dipolarophile is present, are transformed into a purple dye **106**, called *Ruhemann's purple*, through a transamination into imine tautomers **105**. This ninhydrin

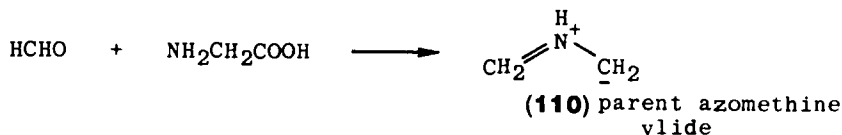


reaction is useful for the detection and quantitative estimation of α -amino acids. The protonated form of Ruhemann's purple offers a rare example of isolable N-unsubstituted azomethine ylide structure **107** (86CC421).

Decarboxylative condensation of N-unsubstituted α -amino acids with benzaldehyde as an aromatic aldehyde requires somewhat harsher conditions. Benzaldehyde and α -amino acids are heated under reflux in DMF together with *N*-phenylmaleimide. The azomethine ylides **108** generated can be captured as mixtures of several stereoisomeric cycloadducts (84CC180). 1-Aminocyclopentane-1-carboxylic acid undergoes a similar reaction with pyridine-3-carbaldehyde in the presence of *N*-phenylmaleimide to afford a spirocyclic cycloadduct, the maleimide cycloadduct of azomethine ylide **109** (84CC182).

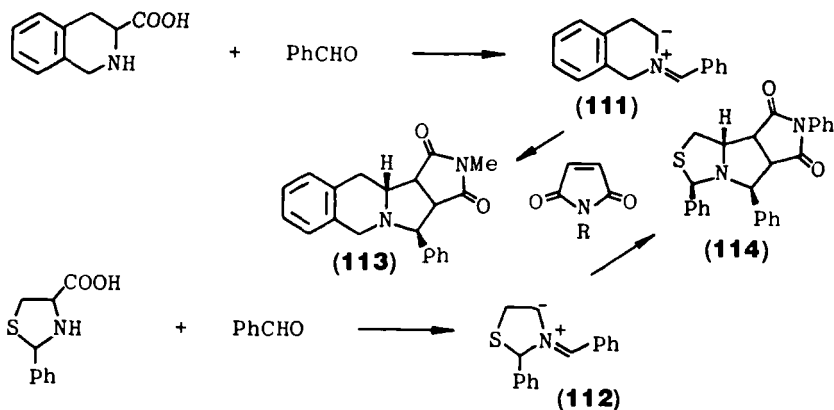


The synthetic utility of azomethine ylide generation through the decarboxylation route has been demonstrated with a variety of additional examples. The use of N-substituted glycines, such as sarcosine, *N*-benzylglycine, *N*-phenylglycine, and *N*-tritylglycine, is most general. These amino acids undergo decarboxylative condensations with aromatic aldehydes, ketones, and formaldehyde (85CC1566; 86CL973; 87BCJ4079). N-Substituted glycine and formaldehyde provide C-unsubstituted azomethine ylides **43** whereas use of glycine itself leads to parent azomethine ylide **110**. Intramolecular trapping reactions of the azomethine ylides generated by the decarboxylation route are also known (84JA7175, 84TL4613). When a 1,2-diketone (isatin) or 1,2,3-triketone (ninhydrin) is used in the condensation, α -substituted α -amino acids (alanine, serine, and histidine) as well as α ,N-disubstituted cyclic α -amino acids (proline and pipercoline), generate reactive azomethine ylides (e.g., **103**)



(84CC180, 84CC182). Later it was discovered that the azomethine ylide generation by the decarboxylation route can be carried out between a wide variety of cyclic α -amino acids and aromatic aldehydes, aliphatic aldehydes, and formaldehyde (87BCJ4079, 87CC47, 87CC49).

Grigg (87CC47, 87CC49) presents an interesting discussion on the stereochemistry of azomethine ylide generation through the decarboxylation route. As shown in the following two examples, the decarboxylative condensation of cyclic α -amino acids with aldehydes leads to a stereoselective generation of (*E,Z*)-azomethine ylides. Thus, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid or 2-phenylthiazoline-4-carboxylic acid reacts with benzaldehyde in the presence of a maleimide to produce a mixture of endo- and exo-cycloadducts, **113** or **114**, derived solely from the (*E,Z*)-ylide **111** or **112**, respectively.



Though the dipole stereochemistry changes depending upon the structure of amino acids, aldehydes, and the reaction temperatures, a kinetic preference for the (*E,Z*)-ylides has been confirmed on the ground of the numerous ylide generations under various conditions. This stereoselective ylide generation is well interpreted by the 5-oxazolidinone mechanism shown in Eq. (16). The condensation of proline as a cyclic α -amino acid with pyridine-2-carbaldehyde would produce thermodynamically favored *trans*-bicyclic lactone intermediate **115**. The decarboxylation of **115** through a concerted cycloreversion leads to (*E,Z*)-azomethine ylide **116**, which isomerizes into thermodynamically more stable (*E,E*)-ylide **117** if the ylide trapping is sluggish. Accordingly, the stereoselectivity depends upon the rate difference between the isomerization and trapping steps.

Azomethine ylide 1,3-dipoles generated through the decarboxylation route are listed in Table V.

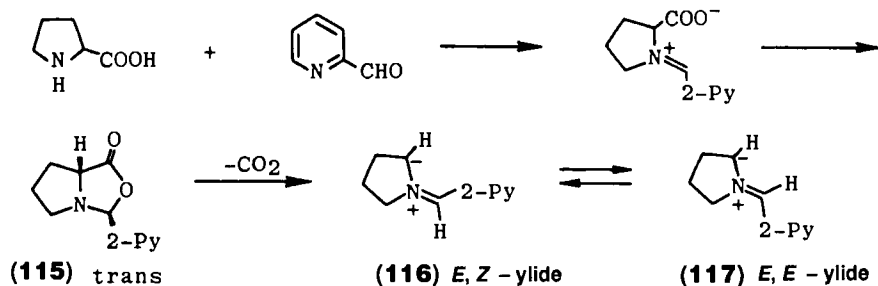


TABLE V
AZOMETHINE YLIDES GENERATED BY THE DECARBOXYLATION ROUTE

Azomethine ylides [$R^1R^2C=NR^+-C^-R^3R^4$]					
R^1	R^2	R^3	R^4	R	Reference
H	H	H	H	H	85CC1566; 87BCJ4079
H	H	H	H	Me	85CC1566; 86CL973; 87BCJ4079
H	H	H	H	PhCH ₂	87BCJ4079
H	H	H	H	Ph ₃ C	87BCJ4079
H	H	H	H	Ph	87BCJ4079
Me	H	H	H	Me	87BCJ4079
Me	Me	H	H	H	86CL973; 87BCJ4079
CF ₃	CF ₃	H	H	Ph	77MI1
CF ₃	CF ₃	H	H	<i>p</i> -MeOC ₆ H ₄	77MI1
CF ₃	CF ₃	H	H	<i>p</i> -MeC ₆ H ₄	77MI1
CF ₃	CF ₃	H	H	<i>p</i> -ClC ₆ H ₄	77MI1
$R^1R^2 = (CH_2)_5$		H	H	H	87BCJ4079
$R^1R^2 = (CH_2)_4$		H	H	Me	86CL973; 87BCJ4079
$R^1R^2 = (CH_2)_5$		H	H	Me	86CL973; 87BCJ4079
$R^1R = (CH_2)_3, R^2 = H$		H	H	—	87BCJ4079
$R^1R = CH_2SCH_2, R^2 = H$		H	H	—	87BCJ4079
$R^1R = (CH_2)_3, R^2 = H$		<i>t</i> -Bu	H	—	76CSR377
$R^1R = o-COC_6H_4CH_2, R^2 = R^4 = H, R^3 = CH_2CH_2Ph$			H	—	87CC47
$R^1R^2 = (CH_2)_5, R^3R = (CH_2)_3$			H	—	76CSR377
Ph	H	H	H	H	84CC180
Ph	H	H	H	Me	70JOC2069; 86CL973; 87BCJ4079
<i>o</i> -AllyloxyC ₆ H ₄	H	H	H	Me	84JA7175
Ph	H	Me	H	H	84CC180; 87CC47; 87CC49
Ph	H	PhCH ₂	H	H	87CC49
Ph	H	MeSCH ₂ CH ₂	H	H	87CC49
Ph	H	$R^3 = 2,6\text{-di-Me-5-heptenyl}, R^4 = R = H$			84CC180

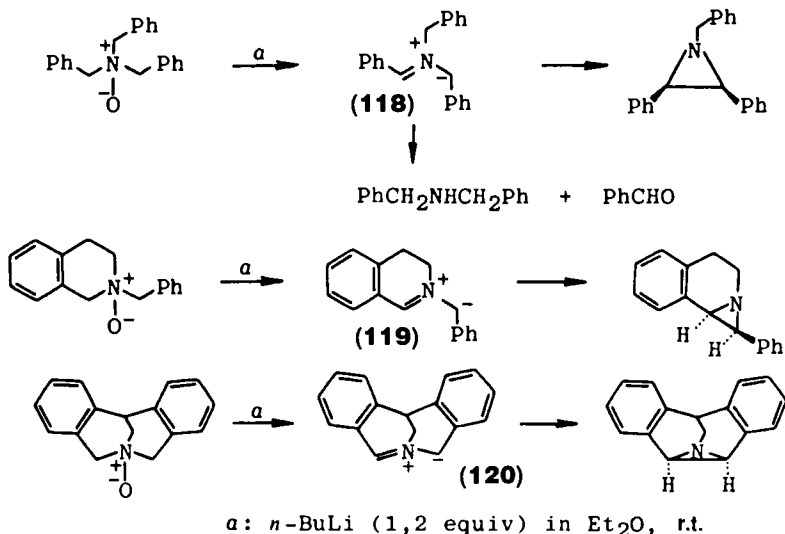
TABLE V (Continued)

Azomethine ylides [$R^1R^2C=NR^+-C^-R^3R^4$]					
R^1	R^2	R^3	R^4	R	Reference
Ph	H	Ph	H	H	84CC180
Ph	H	$R^3R^4 = (CH_2)_4$	H	H	84CC182
Ph	H	$R^3R^4 = (CH_2)_5$	H	H	84CC182
Ph	H	$R^3R = CH_2SCH_2$, $R^4 = H$			87CC47
Ph	H	$R^3R = CH_2SCHPh$, $R^4 = H$			87CC47
Ph	H	$R^3R = o-COC_6H_4CH_2$, $R^4 = H$			87CC47
Ph	H	$RR^3 = o-(CH_2)_2C_6H_4$, $R^4 = H$			87CC49
Ph	H	$R^3R = 3-CH_2-2-InCH_2$, $R^4 = H$			87CC47
Ph	H	$RR^3 = 3-(CH_2)_2-2-In$, $R^4 = H$			87CC47
Ph	$R^2 = R^4 = R = H$, $R^3 = 3-OH-5-HOCH_2-2-Me-4-Py$				84CC182
<i>p</i> -Me ₂ NC ₆ H ₄	H	$R^3R = o-COC_6H_4CH_2$, $R^4 = H$			87CC49
<i>p</i> -NO ₂ C ₆ H ₄	H	$R^3R = o-CH_2C_6H_4CH_2$, $R^4 = H$			87CC49
2-Py	H	$R^3R^4 = (CH_2)_4$	H		84CC182
2-Py	H	$R^3R^4 = (CH_2)_5$	H		84CC182
2-Py	H	$R^3R = (CH_2)_3$, $R^4 = H$			87CC47
2-Py	H	$R^3R = (CH_2)_4$, $R^4 = H$			87CC47
2-Py	H	$R^3R = CH_2SC(Me)_2$, $R^4 = H$			87CC47
2-Py	H	$RR^3 = o-(CH_2)_2C_6H_4$, $R^4 = H$			87CC49
Ph	Ph	H	H	Me	70JOC2069
MeCO	H	H	H	Ph	87BCJ4079
PhCO	H	H	H	Me	84CC182
$R^1R^2 = o-CONHC_6H_4$		Ph	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		H	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		Me	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		CH ₂ OH	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		3-InCH ₂	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		Ph	H	H	84CC180
$R^1R^2 = o-COC_6H_4CO$		$R^3R = (CH_2)_3$, $R^4 = H$			84CC182
$R^1R^2 = o-CONHC_6H_4$		$R^3R = (CH_2)_4$, $R^4 = H$			84CC182

F. N-OXIDE ROUTE

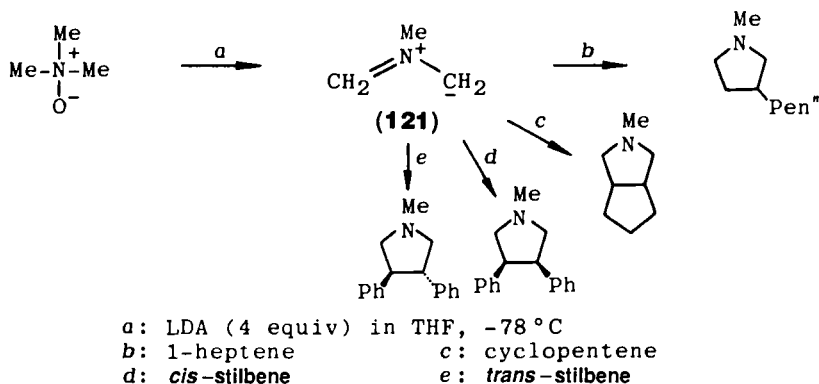
As a new preparative method for aziridines, Takayama and Nomoto have investigated the reaction of aliphatic tertiary amine N-oxides with a strong base such as butyllithium (82CC408). Treatment of tribenzylamine N-oxide with butyllithium (1.2 equivalent) in diethyl ether at 0°C gives *cis*-1-benzyl-2,3-diphenylaziridine as a major product together with dibenzylamine and benzaldehyde. The intermediacy of azomethine ylide 1,3-dipole **118** was suggested, but the cycloaddition trapping with an excess of dipolarophile (unspecified) failed. *N*-Benzyl-1,2,3,4-tetrahydroisoquinoline N-oxide and

6,12-methanodibenzo[*c,f*]azocine *N*-oxide are similarly dehydrated, leading to cyclic **119** and bicyclic azomethine ylide **120**, respectively. They are isolated as *cis*-aziridines. The cyclization of *cis*-azomethine ylide **119**, the only possible configuration, producing the corresponding *cis*-aziridine, would show the radical character of ylide **120**.

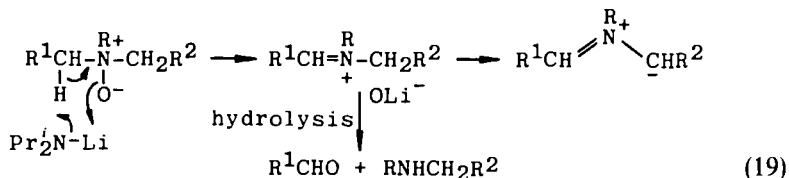


A reaction of trimethylamine *N*-oxide with a large excess of lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C generates C-unsubstituted azomethine ylide **121**. The ylide intermediate **121** is reactive so as to undergo smooth cycloadditions to nonactivated olefinic dipolarophiles, such as 1-alkene, cyclic alkenes, styrene, (*E*)- and (*Z*)-stilbene, to give a variety of pyrrolidines (83CC31). This unusually high reactivity is noteworthy since stabilized azomethine ylides can cycloadd only to electron-deficient dipolarophiles. Even the same ylide (**121**) generated by the decarboxylation route (Section II,E) (85CC1566; 86CL973; 87BCJ4079) and analogous C-unsubstituted azomethine ylides (83TL3447; 84CL1117; 85CPB896, 85CPB2762) are far less reactive than the ylide **121** generated by the present method. Although it is readily understood that electron-deficient olefins would not be able to withstand the highly basic conditions under which the present ylide generation has been performed, the reason for the extremely enhanced reactivity of the ylide **121** remains unsolved. The preparation method for azomethine ylides by dehydrating tertiary amine *N*-oxides with strong bases is referred to as the *N*-oxide route.

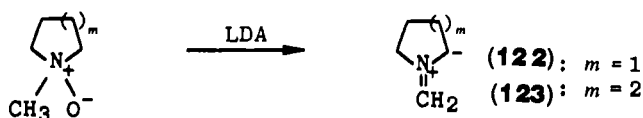
Details of ylide generation through the *N*-oxide route have been reported by Roussi (85CJC725); the proposed reaction mechanism is illustrated in



Eq. (19). A tertiary amine N-oxide is O-lithiated and α -deprotonated with LDA, and the elimination of LiO^- follows immediately to form an iminium intermediate. The second α' -deprotonation of the iminium intermediate generates an azomethine ylide 1,3-dipole. Hydrolysis of the iminium or azomethine ylide 1,3-dipole. Hydrolysis of the iminium or azomethine ylide intermediate on a work-up procedure gives the aldehyde and secondary amine.



Deprotonation of *N*-methylpiperidine *N*-oxide with LDA in THF at -78°C takes place regioselectively on the least crowded methyl carbon to generate azomethine ylide **122** (85JOC2910). Ylide **122** is again highly reactive toward nonactivated olefins such as ethene, cyclopentene, styrene, (*E*)- and (*Z*)-stilbene, and (*E*)- β -methoxystyrene.



Similarly, treating *N*-methylpyrrolidine *N*-oxide with LDA in THF at 0°C in the presence of various olefins generates azomethine ylide **123** by a regioselective deprotonation of the methyl carbon (85H653). Ylide **123** is also accessible through the decarboxylative condensation between proline and paraformaldehyde (87BCJ4079), but an extremely high reactivity of the N-oxide-made azomethine ylide **123** has been observed again. The smooth cycloaddition reactions with cyclopentene, (*E*)-1,2-bis(dimethoxymethyl)ethene,

TABLE VI
 AZOMETHINE YLIDES GENERATED BY THE N-OXIDE ROUTE

Azomethine ylide [$R^1R^2C=NR^+-C^--R^3R^4$]					
R^1	R^2	R^3	R^4	R	Reference
H	H	H	H	Me	83CC31; 85CJC725
H	H	H	H	Ph	85CJC725
H	H	H	H	2,4,6-Me ₃ C ₆ H ₂	85CJC725
$R^1R = (CH_2)_3$	H	H	H	—	85H653
$R^1R = (CH_2)_4$	H	H	H	—	85JOC2910
Ph	H	H	H	Me	85CJC725
Ph	H	Ph	H	Me	85CJC725
Ph	H	Ph	H	<i>n</i> -Bu	82CC408
Ph	H	Ph	H	PhCH ₂	82CC408; 85CJC725
Ph	H	Ph	H	<i>c</i> -Hex	82CC408
Ph	H	<i>p</i> -MeOC ₆ H ₄	H	<i>c</i> -Hex	82CC408
<i>p</i> -ClC ₆ H ₄	H	<i>p</i> -ClC ₆ H ₄	H	<i>c</i> -Hex	82CC408
Ph	H	$RR^3 = o-(CH_2)_2C_6H_4$, $R^4 = H$			82CC408
<i>o</i> -RC ₆ H ₄	H	<i>o</i> -RC ₆ H ₄	H	$-CH_2CHR^1R^3$	82CC408

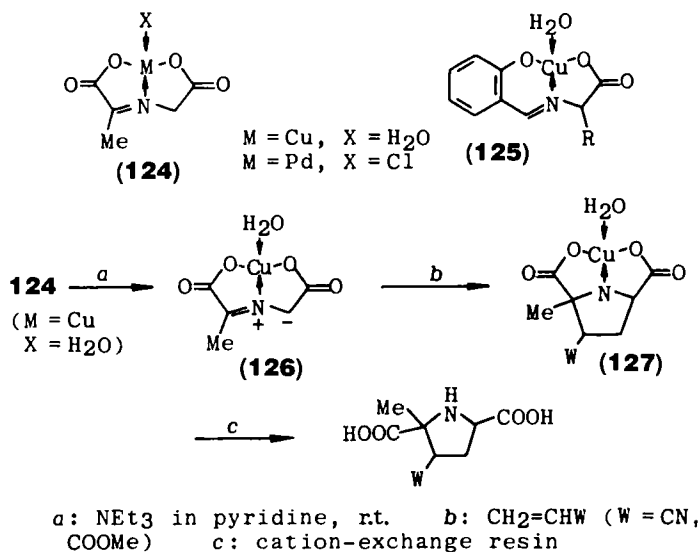
styrene, and (*E*)- and (*Z*)-stilbene take place stereospecifically. However, regioselectivity in the cycloadditions with styrene and 2-propen-1-ol was poor.

Although structural modification is quite limited, the azomethine ylides generated by the N-oxide route are complementary in their applications in organic synthesis to the identical ylides generated by other methods [e.g., the decarboxylation route (Section II,E) and the desilylation route (Section II,B)]. When the origin of the enhanced reactivity is solved, a new field will be open in the chemistry of azomethine ylide 1,3-dipoles.

Azomethine ylide 1,3-dipoles generated through the N-oxide route are summarized in Table VI.

G. N-METALLATION ROUTE

The imines derived from α -amino acids and pyruvic acid or salicylaldehyde coordinate to copper (II) (67BCJ1536) and palladium(II) metals (68BCJ255) to form stable, isolable bicyclic metal complexes **124** and **125**. Complex formation increases the acidity of the α hydrogen, so that the activated hydrogen can be deprotonated by a weak base. The resulting anionic species have been employed for α for α -alkylation (67BCJ2212) or for condensation with aldehydes (70JA5514; 71TL79). These reactions offer an important method for the α -substitution of α -amino acids without N- and O-protection.

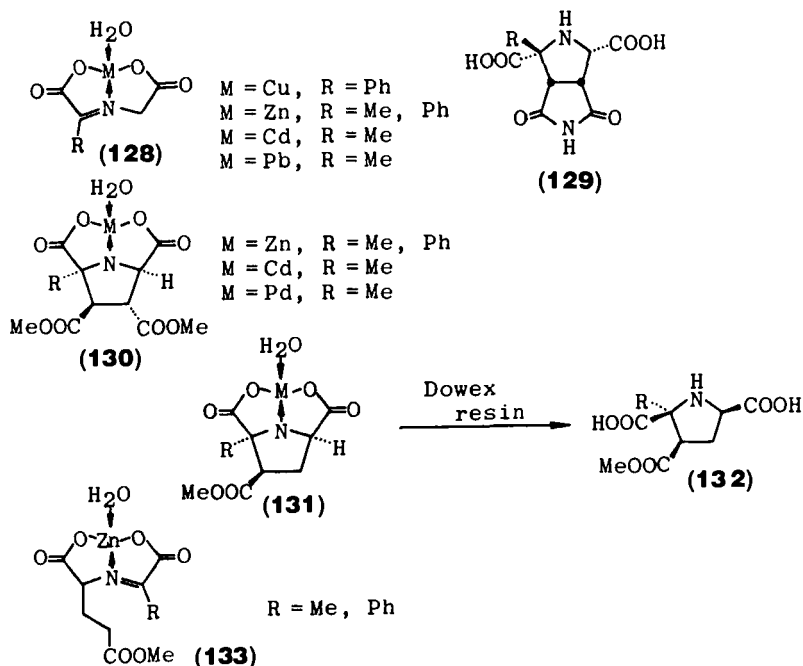


Casella found that treatment of *N*-pyruvylideneglycinatocopper(II) (**124**) ($\text{M} = \text{Cu}$, $\text{X} = \text{H}_2\text{O}$) with triethylamine in pyridine generates an anionic species that can be captured with acrylonitrile or methyl acrylate (79S150). The isolated products are not the Michael-type adducts, but rather the copper chelates (**127**) of pyrrolidine-2,5-dicarboxylic acids, which correspond to the cycloadducts of *N*-metallated azomethine ylides **126**. Removal of the copper metal from **127** through Dowex 50W (H^+ form) resin gives regiochemically pure pyrrolidine-2,5-dicarboxylic acids as mixtures of several stereoisomers. The poor stereospecificity seems to be inconsistent with the tight structure expected for the chelated azomethine ylide species **126** bearing two carboxyl groups cis to each other. Later, similar trapping reactions of ylide **126** using other olefinic dipolarophiles, such as acrolein, 3-buten-2-one, dimethyl maleate, dimethyl fumarate, and maleimide, provided stereoisomeric mixtures of the cycloadducts, after demetallation through the Dowex resin column (82JCS(P1)1827). Based upon all these data, the poor stereoselectivity was concluded to arise from an epimerization process during demetallation.

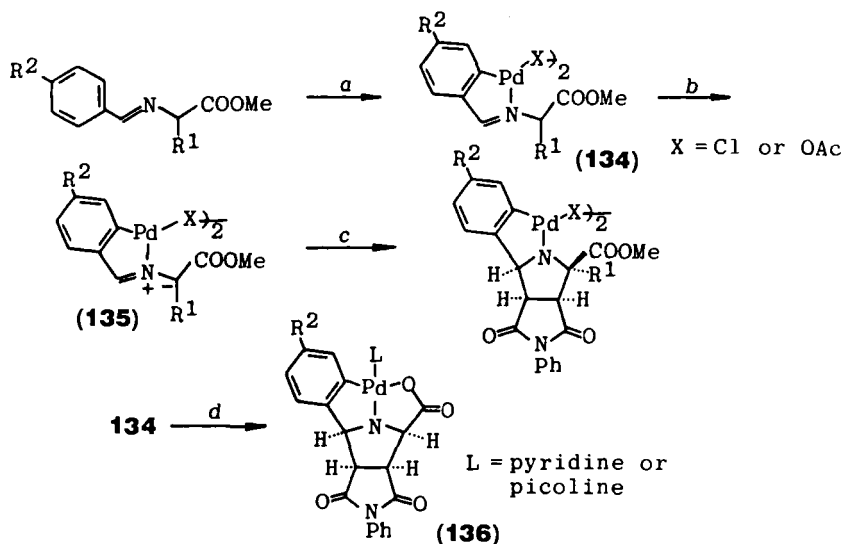
Metals other than copper(II) are also incorporated into the glycineimines of pyruvic acid or phenylglyoxylic acid to give further isolable chelates **128** containing zinc(II), cadmium(II), and lead(II) (86JCS(P1)1669). The reaction of copper(II) chelate **124** ($\text{X} = \text{Cu}$, $\text{X} = \text{H}_2\text{O}$) with maleimide in the presence of triethylamine affords a single stereoisomer of cycloadduct **129** after a demetallation procedure through the cation-exchange resin; a similar deprotonation of other chelates **128** ($\text{M} = \text{Zn}$, Cd , Pb) with triethylamine is followed by an anion-trapping cycloaddition with dimethyl fumarate to lead to

stereoselective formation of the cycloadduct chelates **130**. The high stereoselectivity makes a striking contrast with Casella's results. The selectivity was found to depend upon the reaction time, as shown in an epimerization example in which **130** ($M = \text{Zn}$, $R = \text{Me}$) changes into a 2:1 mixture of two stereoisomers on treatment with triethylamine (1 equivalent) in pyridine at room temperature (86JCS(P1)1669). The reactions of **124** ($M = \text{Cu}$, $X = \text{H}_2\text{O}$) and **128** ($M = \text{Zn}$, $R = \text{Ph}$) with methyl acrylate also produce regio- and stereoselective cycloadducts **131** ($M = \text{Cu}$, $R = \text{Me}$; $M = \text{Zn}$, $R = \text{Ph}$), which are then stereospecifically demetallated into **132**. However, a mixture of two stereoisomeric cycloadducts **132** is obtained when a large amount of resin or recycled resin is used in the demetallation step of **131**. Regioselectivity in the reaction of **128** with acrylonitrile or a vinyl sulfone has been also discussed. The Michael addition mechanism previously proposed by Casella (82JCS(P1)1827) for the base-induced cycloadditions of the metal chelates **124** and **128** has been questioned by Grigg (86JCS(P1)1669), who suggests the involvement of N-metallated azomethine ylides (e.g., **126**), since the zinc chelates **133** prepared from glutamic acid do not cyclize into **131** ($M = \text{Zn}$) under the cycloaddition conditions.

More recently, another route to N-metallated azomethine ylides has been presented. The *N*-(*p*-substituted benzylidene) imines of α -amino esters are

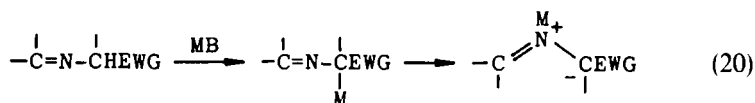


converted into the *o*-palladated dimeric complexes **134** by treatment with palladium acetate in hot acetic acid or with lithium tetrachloropalladate in methanol (86CC631). The complexes **134** are readily deprotonated with triethylamine in dichloromethane to generate a red solution of N-metallated azomethine ylides **135**, which are captured with *N*-phenylmaleimide as an endo-selective dimeric cycloadduct. Use of pyridine or picoline as a solvent in the ylide generation and cycloaddition sequence of **134** results in the formation of monomeric cycloadducts **136** via a ligand-exchange reaction and ester hydrolysis.



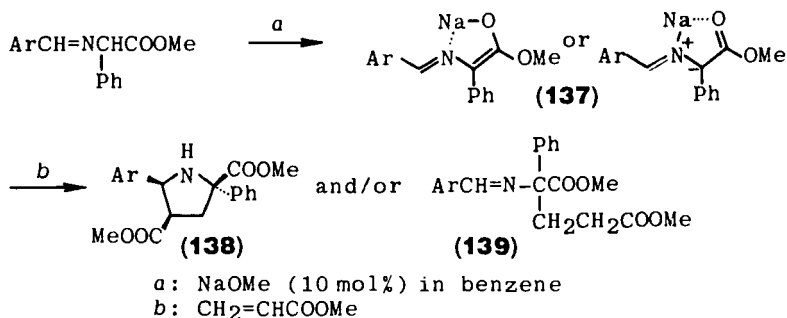
a: $Pd(OAc)_2$ in AcOH or $LiPdCl_4$ in MeOH b: NEt_3 in CH_2Cl_2
 c: *N*-phenylmaleimide d: NEt_3 + *N*-phenylmaleimide in pyridine or picoline

Simple α -metallation of the imines bearing an electron-withdrawing α substituent will generate the α -metallated imines. According to the concept of the tautomerization route (Section II,C), a 1,2-metal migration should be followed to generate N-metallated azomethine ylides [Eq. (20)]. Although it is quite hard to tell the difference between N-metallated azomethine ylide 1,3-dipoles from 2-azaallyl anion species that have been investigated intensively by Kauffmann (74AG(E)627), anionic species are not included as N-metallated azomethine ylides if they undergo cycloadditions only to nonactivated olefins



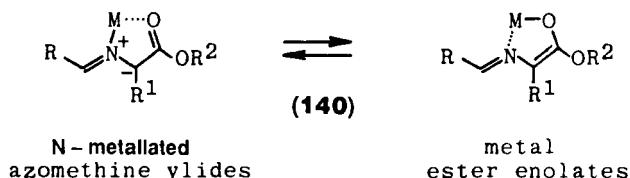
such as aryl-substituted olefins and acetylenes. If anionic species generated by the α -metallation of imines show high reactivity toward electron-deficient activated dipolarophiles, these intermediates resemble stabilized azomethine ylides with respect to their chemical properties. Accordingly, such metallated species are regarded here as N-metallated azomethine ylides.

Methyl *N*-furfurylidene- α -phenylglycinate reacts with methyl acrylate in the presence of a catalytic amount (0.1 equivalent) of sodium methoxide in benzene to give a regio- and stereoselective cycloadduct **138** (Ar = 2-furyl) (80CC648). In similar reactions using the related imines derived from other aromatic aldehydes, the regio- and stereoselective cycloaddition competes with the Michael addition giving **139**. However, the Michael adducts **139** are found not to be precursors of the cycloadducts **138** under the base-induced reaction conditions. On the basis of the exclusively high selectivity, it is most likely that the anionic intermediate involved in the above reactions would be something like sodium enolate or N-metallated azomethine ylide **137**.

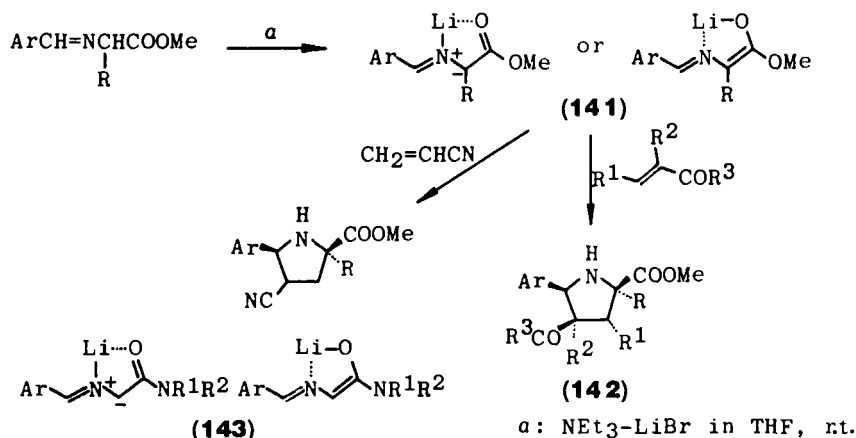


N-Metallated azomethine ylides **140** of ester-stabilized types are tautomeric to the metal ester enolates (**141**) of chelate-stabilized types. The only structural difference is which heteroatom between the imine nitrogen and the ester carbonyl oxygen is connected with the metal (M) by a covalent bond. The difference in chemical properties expected for the ylidic forms **140** and enolate forms **141** is not yet clear.

In the presence of lithium bromide in THF the imines of α -amino esters can be deprotonated with triethylamine at room temperature to generate highly reactive 1,3-dipoles **141**, which exist either in an N-lithiated azomethine



ylide structure or in a chelated lithium enolate form (88JOC1384). The cycloaddition trapping of **141** can be carried out, without any trouble because of the weakly basic conditions, with a variety of olefins such as maleimides, maleates, fumarates, acrylates, crotonates, methacrylates, and vinyl ketones. When strong bases such as butyllithium and LDA are used for the α -metallation of α -amino ester imines, activated electron-deficient olefins suffer from an anion-induced polymerization even at -78°C . The corresponding cycloadducts **142** are obtained in a highly regio- and stereoselective fashion. Since similar cycloadditions of ylides **141** ($\text{R} = \text{H}, \text{Me}$) to acrylonitrile are nonstereoselective, it would be possible that the lithium metal on the imine nitrogen is stabilized by a chelation to the carbonyl oxygen of the dipolarophiles. Generation of similar 1,3-dipoles **143** from the imines of α -amino amides is also possible (88JOC1384).



The imines of α -aminonitriles are lithiated with butyllithium or LDA at -78°C in THF. The anionic intermediates **144** generated are captured in the regio- and stereoselective, and stereospecific cycloaddition with a number of olefins to give 4,5-cis-1-pyrrolines **145** after the elimination of lithium cyanide

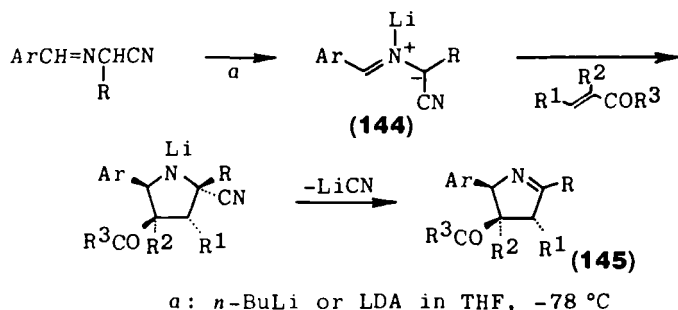


TABLE VII
AZOMETHINE YLIDES GENERATED BY THE N-METALLATION ROUTE

Azomethine ylide $[R^1R^2C=NM^+-C^-R^3R^4]$					
R^1	R^2	R^3	R^4	Metal	Reference
COOMe	H	Ph	H	Li	88JOC1384
COOMe	Me	Ph	H	Li	88JOC1384
COOMe	<i>i</i> -Pr	Ph	H	Li	88JOC1384
CO[N(CH ₂) ₄]	H	Ph	H	Li	88JOC1384
CONBu- <i>t</i>	H	Ph	H	Li	88JOC1384
COOMe	Ph	2-Furyl	H	Na	80CC648
CN	H	Ph	H	Li	87BCJ3359
CN	H	Ph	H	Li(LiI)	87BCJ3359
CN	H	Ph	H	Li(NEt ₃)	87BCJ3359
CN	H	Ph	H	MgBr	87BCJ3359
CN	H	Ph	H	MgN(<i>i</i> -Pr) ₂	87BCJ3359
CN	Me	Ph	H	Li	87BCJ3359
CN	<i>i</i> -Pr	Ph	H	Li	87BCJ3359
CN	Ph	Et	H	Li	87BCJ3359
CN	Ph	Ph	H	Li	87BCJ3359
COOM	Me	COOM	H	Zn(II)(H ₂ O)	86JCS(P1)1669
COOM	Ph	COOM	H	Zn(II)(H ₂ O)	86JCS(P1)1669
COOM	Me	COOM	H	Cd(II)(H ₂ O)	86JCS(P1)1669
COOM	Me	COOM	H	Pb(II)(H ₂ O)	86JCS(P1)1669
COOM	Me	COOM	H	Cu(II)(H ₂ O)	79S150; 82JCS(P1)1827; 86JCS(P1)1669
COOM	Ph	COOM	H	Cu(II)(H ₂ O)	86JCS(P1)1669
COOMe	H	$R^3 = 2\text{-M-4-}(i\text{-Pr})\text{-C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(Cl)-	86CC631
COOMe	Me	$R^3 = 2\text{-M-4-}(i\text{-Pr})\text{-C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(Cl)-	86CC631
COOMe	PhCH ₂	$R^3 = o\text{-MC}_6\text{H}_4$, $R^4 = \text{H}$		Pd(Cl)-	86CC631
COOMe	<i>i</i> -Pr	$R^3 = 2\text{-M-4-}(i\text{-Pr})\text{-C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(Cl)-	86CC631
COOMe	<i>i</i> -PrCH ₂	$R^3 = 2\text{-M-4-}(i\text{-Pr})\text{-C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(Cl)-	86CC631
COOMe	Ph	$R^3 = o\text{-MC}_6\text{H}_4$, $R^4 = \text{H}$		Pd(OAc)-	86CC631
COOMe	Ph	$R^3 = 2\text{-M-4-NO}_2\text{C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(OAc)-	86CC631
COOEt	H	$R^3 = 2\text{-M-4-}(i\text{-Pr})\text{-C}_6\text{H}_3$, $R^4 = \text{H}$		Pd(Cl)PPh ₃	86CC631

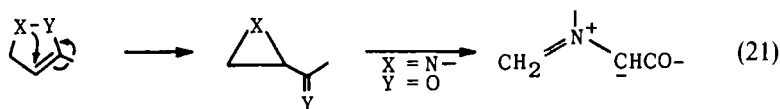
(87BCJ3359). Unlike the N-metallated species **141** and **143** derived from the imines of α -amino esters or amides, the lithium metal is presumably sitting on the imine nitrogen so that **144** can be classified as an N-metallated azomethine ylide. In the cycloaddition step, the chelation of the lithium metal to the carbonyl oxygen of dipolarophiles is again important for the high regio- and stereoselectivities. This will be discussed later (Sections III,C and B).

Azomethine ylide 1,3-dipoles generated through the N-metallation route are listed in Table VII.

H. OXAZOLINE ROUTE

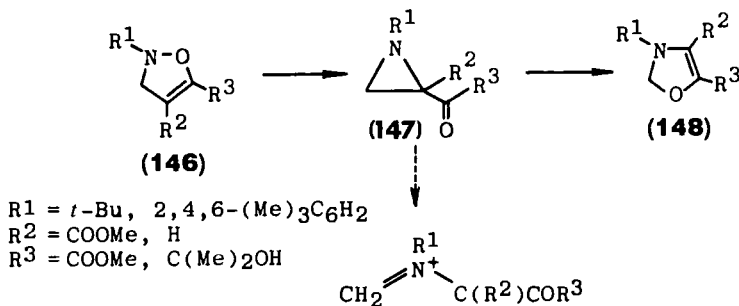
Generation of azomethine ylides by starting from oxazoline heterocycles consists of the following steps: (1) valence isomerization of 4-isoxazolines, (2) valence isomerization of 4-oxazolines, and (3) cycloreversion of 5-oxazolidinones or oxazolidines. These three generation methods as variations of the *oxazoline route* are reviewed in this section.

When two heteroatoms of greater electronegativity than carbon are linked to each other, such a linkage is readily cleaved. This is the principle for the generation of carbonyl-stabilized azomethine ylides by a thermal ring opening of 4-isooxazolines [Eq. (21)].

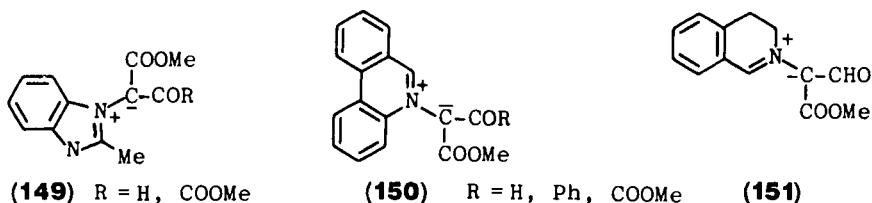


A possibility for azomethine ylide generation from 4-isoxazolines was first suggested by Baldwin, who demonstrated a thermal N—O bond cleavage of 4-isoxazoline systems (68JA5325). Cycloaddition of *N*-methylene(*t*-butyl)-amine *N*-oxide to dimethyl acetylenedicarboxylate takes place at 0°C, rapidly and quantitatively, to give 4-isoxazoline **146** ($\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{R}^3 = \text{COOMe}$), which isomerizes at 80°C into 4-oxazoline **148** ($\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{R}^3 = \text{COOMe}$). The nitron bearing an *N*-aryl substituent and the same acetylene directly afford 2-acylaziridine **147** ($\text{R}^1 = 2,4,6\text{-trimethylphenyl}$, $\text{R}^2 = \text{R}^3 = \text{COOMe}$). Reaction of the *N*-*t*-butylnitron with 3-methylbutyn-3-ol at 74°C produces labile 4-isoxazoline **146** [$\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{C}(\text{Me})_2\text{OH}$], which isomerizes at 78°C to 2-acylaziridine **147** [$\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{C}(\text{Me})_2\text{OH}$]. These results have unveiled a sequence of 4-isoxazoline isomerizations into 4-oxazolines via 2-acylaziridines. As has been discussed above (Section II,A) 2-acylaziridines are important precursors of acyl-stabilized azomethine ylides through a thermal ring-opening reaction. Accordingly, 4-isoxazolines would also be nice precursors of azomethine

ylides (83CRV241). The synthetic value of this generation method relies on the ready availability of the starting 4-isoxazolines, which can be prepared by cycloaddition reactions of nitrones with acetylenes (69CB904; 78TL1463; 83CRV241).

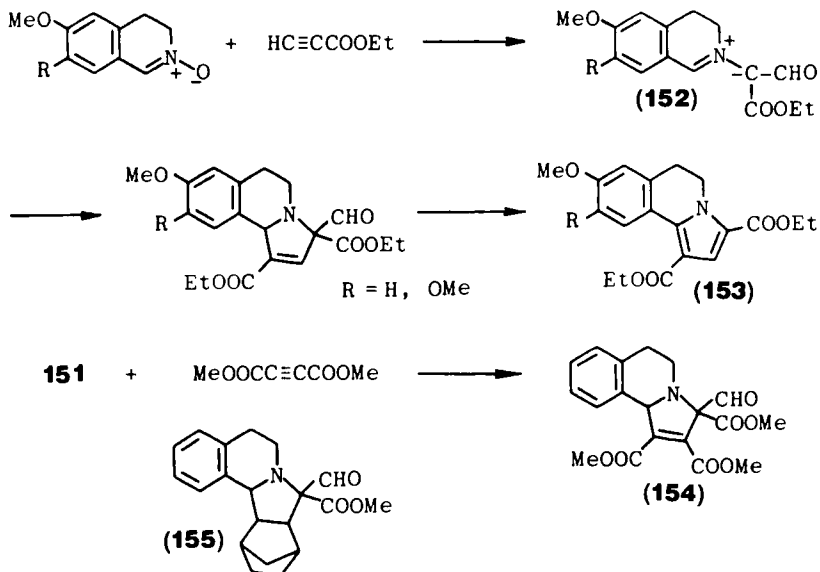


Very often the azomethine ylides generated by a thermal isomerization of 4-isoxazolines are highly stabilized and sometimes isolable. Activated acetylenes, such as acetylenedicarboxylates, are employed in the cycloaddition with nitrones leading to the azomethine ylides bearing two acyl moieties on one carbon, as shown in **149**–**151** (65JOC1118; 67JCS(C)2066; 69CB904). Only quite limited examples are known for the cycloaddition trapping of the azomethine ylides generated by this route.



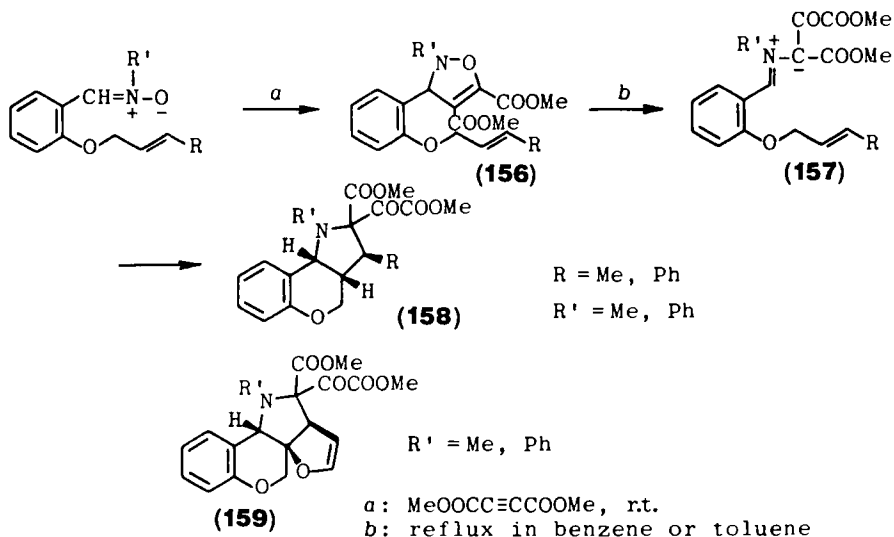
Kano treated 3,4-dihydroisoquinoline N-oxides with two equivalents of ethyl propiolate in refluxing benzene and obtained dihydrobenzo[*g*]-indolizines **153** (82H2143). The supposed intermediates are the 4-isoxazoline-derived stable azomethine ylides **152** and the cycloadducts of **152** to the propiolate.

Huisgen has shown that highly stabilized and isolable azomethine ylides are not always inert to dipolarophiles (84H21). Isolable ylide **151** undergoes a quantitative cycloaddition with dimethyl acetylenedicarboxylate in 1 hr at 20°C to furnish **154**. With norbornene, a 1:1 diastereomeric mixture of **155** has been isolated, indicating that the highly stabilized azomethine ylide **151** is even more reactive to nonactivated olefins than the azomethine ylides with a medium stabilization. This fact is consistent with the high reactivity of highly



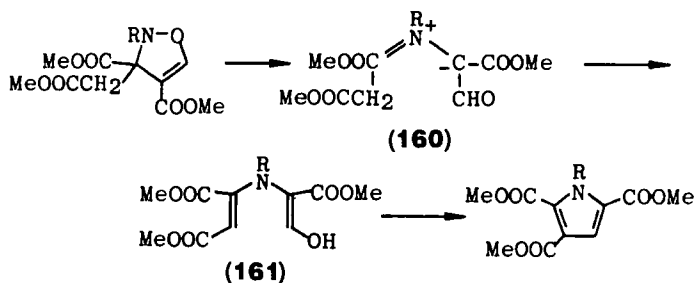
stabilized aromatic N-ylides toward nonactivated and electron-rich olefins (87UP1).

An increased reactivity of such ylides to nonactivated olefins is shown in the following intramolecular ylide trapping. The highly stabilized azomethine ylides **157**, which are thermally generated by heating 4-isoxazolines **156**

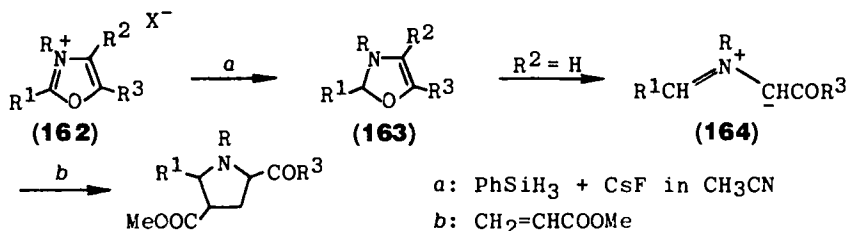


bearing an olefin-trapping agent, undergoes an intramolecular cycloaddition to give **158** in high yields (84CL797). It is surprising that even the inactive double bond of the furan ring reacts with the extremely stabilized ylides affording heteropropellanes **159**.

When 4-isoxazolines with an alkyl substituent carrying an acidic α -hydrogen at the 3-position undergo a thermal valence isomerization into azomethine ylides **160**, the acidic α hydrogen migrates to the anionic center to form enolated bisenamine intermediates **161** (70CB3196). A process similar to the cyclization of **161** providing pyrroles was discussed in Section II,A.



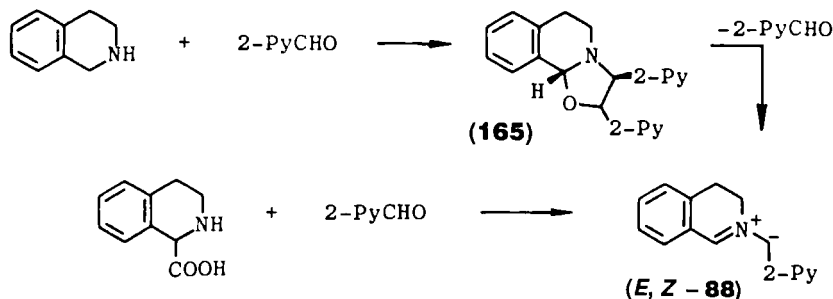
As discussed above, a valence tautomerism starting from 4-isoxazolines **146** reaches 4-oxazolines **148** via 2-acylaziridines **147**, in which one can find a junction to the route leading to azomethine ylides. Compared to the ready availability of 4-isoxazolines by the nitrone or N-oxide cycloadditions with acetylenes, 4-oxazolines are relatively inaccessible. They have been made directly or indirectly by an acylaziridine pyrolysis. A convenient synthetic method of 4-oxazolines has been discovered by Vedejs (86JA6433). Readily available oxazolium salts **162** can be selectively reduced with $\text{PhSiH}_3/\text{CsF}$. Overreduction is easily avoided when this reduction is conducted in the presence of dipolarophiles. The 4-oxazolines **163** opened at room temperature to generate azomethine ylides **164**, which are captured in 1,3-dipolar cycloadditions. The stability of 4-oxazolines **163** is strongly influenced by the presence of a substituent at the 4-position. Ring opening of **163** to generate 1,3-dipole **164** occurs rapidly at room temperature when the 4-position is



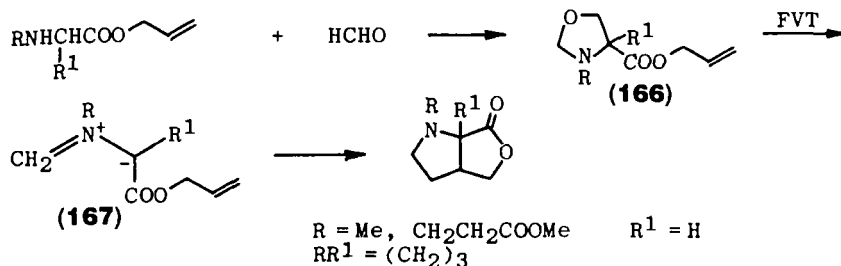
unsubstituted ($R^2 = H$), whereas **163** resists opening to **164** when $R^2 = \text{alkyl}$, aryl, etc.

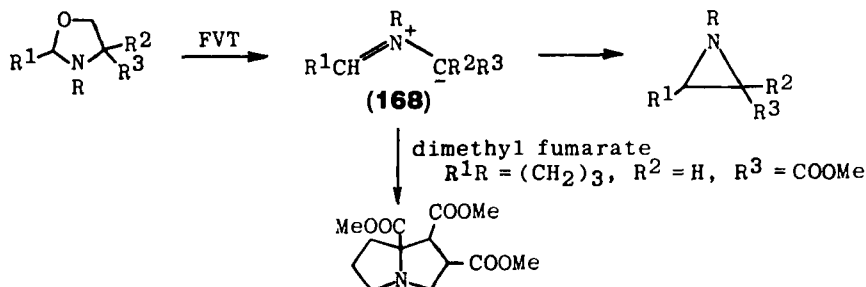
The last variation of the oxazoline route is a cycloreversion of 5-oxazolidinones or oxazolidines. Thermal decarboxylation of 5-oxazolidinones is a convenient method of generating nonstabilized azomethine ylides, since the heterocyclic precursors are accessible, and sometimes isolable, by simply heating α -amino acids and carbonyl compounds. This has been discussed in Section II,E.

A single stereoisomer of ring-fused oxazolidine **165** eliminates a molecule of pyridine-2-carbaldehyde, though the pyrolysis conditions were unspecified, to generate *anti*-azomethine ylide (*E,Z*)-**88** (87CC49), which is captured in the dipolar cycloaddition with *N*-methylmaleimide. The starting oxazolidine **165** is available by an ylide generation and cycloaddition trapping sequence starting from 1,2,3,4-tetrahydroisoquinoline and 2 equivalents of pyridine-2-carbaldehyde (86CC602). Dipole (*E,Z*)-**88** can be directly and stereoselectively generated by the decarboxylation route from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid and pyridine-2-carbaldehyde (87CC49). Therefore, ylide generation by the thermolysis of **165** is synthetically of little importance.



Joucla has reported another example of azomethine ylide generation from oxazolidines by a technique of flash vacuum thermolysis (FVT) (87TL2973). Allyl esters of *N*-substituted α -amino acids react with 2 molar equivalents of paraformaldehyde, under reflux in toluene, to give rise to oxazolidines **166**



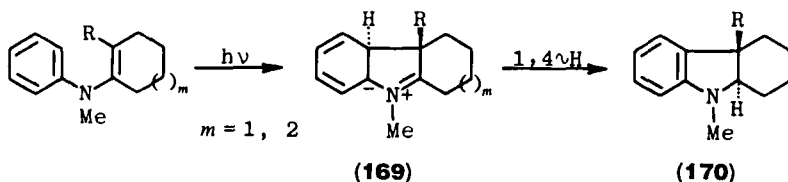


through an ylide generation and cycloaddition sequence. Flash vacuum pyrolysis of **166** has been performed at 500–550°C at 0.005 Torr, the ylide **167** generated being intramolecularly captured. Though this method requires drastic conditions, the reaction can be carried out on a preparative scale. Ring closure of ylide **168** to produce aziridines as well as the intermolecular ylide trapping have also been demonstrated (87TL2975).

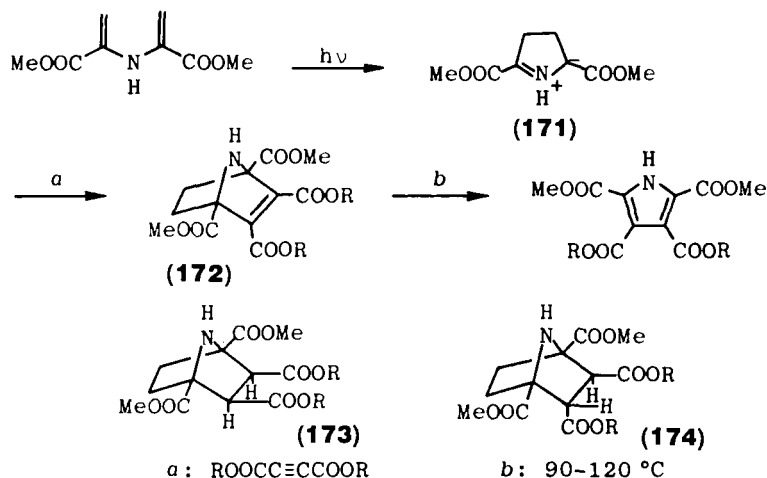
I. MISCELLANEOUS ROUTES

There are further methods of generating azomethine dipoles. As the scope and limitation of these methods are not fully understood so far, they are treated together in this section. In some cases azomethine ylides have been successfully captured in cycloaddition trappings, though quite limited examples are known. In the other cases azomethine ylides are the key intermediates in the reported reaction schemes.

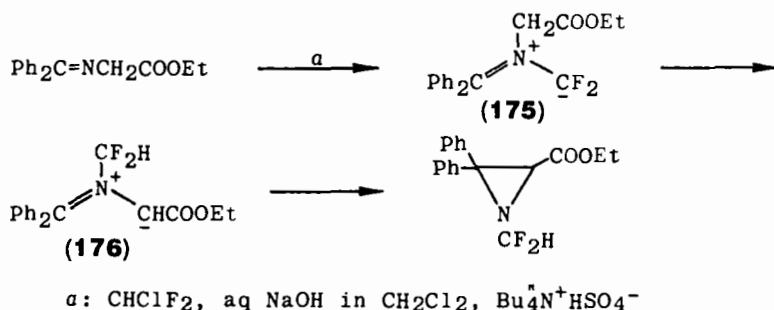
Photochemical cyclization of 1-(*N*-methylanilino)cycloalkenes gives primarily trans-fused hexahydrocarbazole derivatives **170** (68JA5329). This cyclization may involve a conrotatory electrocycloization of divinylamines, followed by a suprafacial [1,4]-sigmatropic hydrogen shift (70CC531). The intermediates in the initial cyclization are believed to be cyclic azomethine ylide 1,3-dipoles **169**, but no direct observation of the participation of such dipoles was made. All attempts to capture dipoles **169** by cycloaddition with maleic anhydride or furan were unsuccessful (71JA2918).



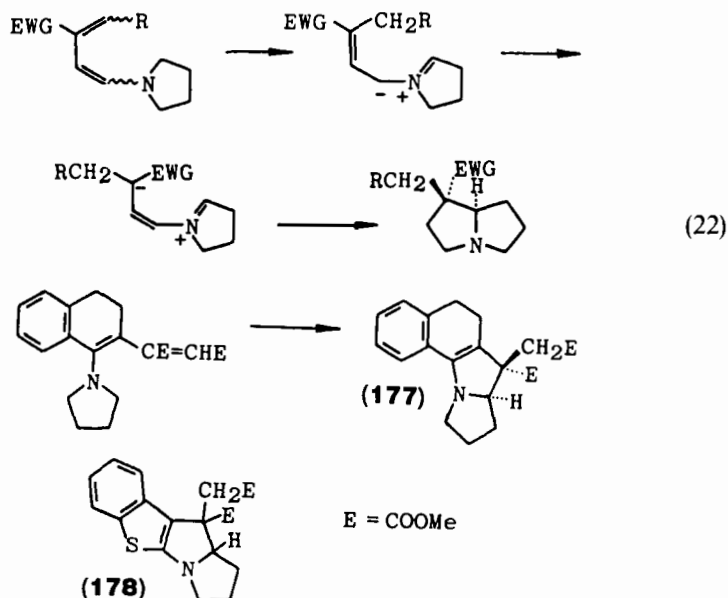
From a synthetic viewpoint, *N*-arylvinylamines are not appropriate as azomethine ylide precursors because the hydrogen shift from the intermediary ylides must be extremely accelerated by the rearomatization of the fused dihydro benzo moiety. Zaima and Mitsuhashi were the first to succeed with synthetic applications of the above photochemical generation method of cyclic azomethine ylides (83JHC1). The substrate employed in their work is bis(1-methoxycarbonylvinyl)amine. Irradiation of this divinylamine in carbon tetrachloride at 18°C in the presence of acetylenedicarboxylates produces excellent yields of 7-azabicyclo[2.2.1]hept-2-ene-1,2,3,4-tetracarboxylates **172**, which correspond to the cycloadducts of the expected azomethine ylide intermediate **171**. Heating the bicyclic cycloadducts **172** at 90–120°C induces a smooth cycloreversion eliminating a molecule of ethene to give pyrrole-2,3,4,5-tetracarboxylates in quantitative yields. The azomethine ylide **171** can be trapped also with olefinic dipolarophiles, such as maleates and fumarates, to furnish stereospecifically 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates **173** and **174**, respectively (84JHC445).



N-Alkylation of imines with a highly electrophilic carbene generates azomethine ylide 1,3-dipoles. The first example was demonstrated in 1987 by McCarthy and O'Donnell (87CC469). A reaction of difluorocarbene, generated from chlorodifluoromethane under ion-pair extraction conditions, with ethyl *N*-(diphenylmethylene)glycinate provided ethyl 1-difluoromethyl-3,3-diphenylaziridine-2-carboxylate. This aziridine formation may involve the initial electrophilic addition of difluorocarbene onto the imine nitrogen generating azomethine ylide **175**, which undergoes a proton migration to lead to the more highly stabilized isomer **176**.



1-Pyrrolidinyl-1,3-butadienes bearing an electron-withdrawing substituent (EWG) at C-3 undergo thermal cyclizations in a stereoselective manner to provide pyrrolizine derivatives (81JOC424). It has been proposed that this unusual ring closure involves the initial generation of vinyl-substituted azomethine ylide intermediates and their stereoselective 1,5-cyclization, as shown in Eq. (22) (83JA4775). One example is the stereoselective cyclization of 1-pyrrolidinyl-2-vinyl-3,4-dihydronaphthalene into naphtho[2,1-*b*]-pyrrolizine **177**. In the thiophene series, two isomeric cyclized products (**178**) were produced, the isomer ratio of which depended upon the polarity of the reaction solvent (83JA4775). So far synthetic versatility of this method, for instance the trappings by cycloaddition of ylides with dipolarophiles, has not been unveiled.



III. Cycloadditions

A. REACTIVITY OF YLIDES

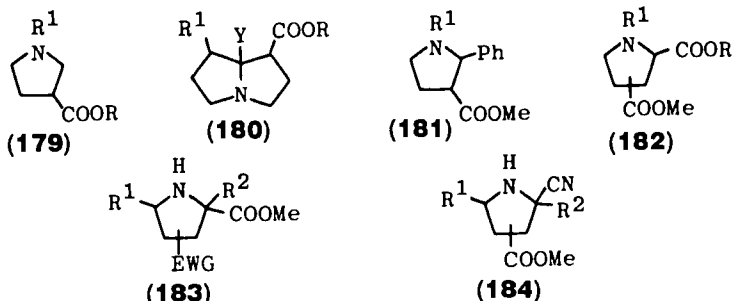
According to the frontier molecular orbital theory (FMO theory), the reactivity of a 1,3-dipole is inversely proportional to the energy difference between the frontier orbitals of a 1,3-dipole and a dipolarophile. The frontier orbital energies of the parent azomethine ylide **110** are calculated by a CNDO/2 method to be highest occupied molecular orbital (HOMO) = -6.9 and lowest unoccupied molecular orbital (LUMO) = 1.4 eV. Due to the narrow frontier orbital separation, ylide **110** will be able to react with both electron-deficient and -rich dipolarophiles (73JA7287). Frontier orbital energies for a variety of dipolarophiles are given as follows (HOMO and LUMO in eV): electron-rich olefins: -8 and 3 ; alkyl-substituted ethenes: -9 and 2 ; conjugated olefins: -9 and 1 ; ethene -10.5 and 1.5 ; electron-deficient olefins: -10.9 and 0 . Ester-stabilized ylide **7** has lower HOMO (-7.7 eV) and LUMO levels (-0.6 eV), so that **7** must be more reactive than the parent ylide **110** both to electron-rich and -poor olefins (73JA7301). With this theoretical analysis in hand, the reported cycloaddition examples of azomethine ylides to a variety of dipolarophiles are reviewed below.

Dipolarophiles most frequently employed in trapping of azomethine ylides are acetylenedicarboxylates and maleimides because they are much more reactive than most other dipolarophiles. Maleic anhydride is almost equal to maleimides in reactivity toward azomethine ylides, and furmarates and maleates rank next. These dipolarophiles are so highly reactive in 1,3-dipolar cycloadditions that most of the azomethine ylides cited in this article can be smoothly trapped as the corresponding cycloadducts. Accordingly, less reactive dipolarophiles are selected in this section in order to evaluate the reactivity of azomethine ylide 1,3-dipoles.

1. *Unsymmetrical Activated Olefins and Acetylenes*

Acrylic dipolarophiles such as acrylonitrile and acrylates have been used very often as unsymmetrically substituted olefinic dipolarophiles. Azomethine ylides **43** of nonstabilized types bearing no substituent on the carbon are accessible by the desilylation route (Section II,B) (84CL1117; 85CPB2762; 87JOC235) or the decarboxylation route (Section II,E) (85CC1566; 86CL973; 87BCJ4079); they undergo smooth cycloadditions to acrylates to give pyrrolidine-3-carboxylates **179**. Similar cycloadditions of C-alkyl-substituted ylides **23** and **25** to acrylates offer a direct synthesis of pyrrolizine-1-carboxylates **180** (80JA7993; 82CPB3167; 83JOC4773;

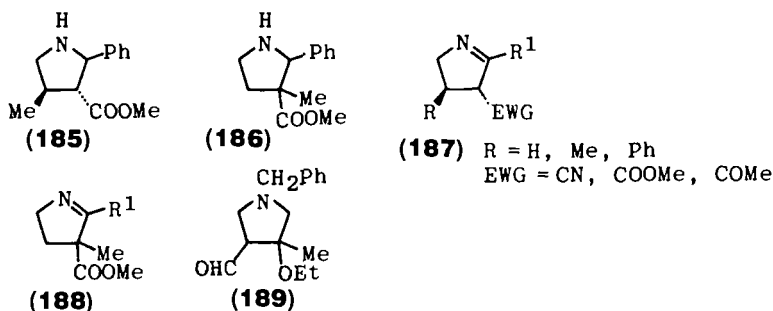
85JOC2170). Nonstabilized azomethine ylides **22** ($R^1 = \text{Ph}$, $R^2 = \text{H}$) carrying a phenyl group as the only C substituent are readily accessible by the desilylation route (Section II,B), and can be regioselectively trapped with methyl acrylate to produce 2-phenylpyrrolidine-3-carboxylates **181** (82TL2589; 83CPB3939; 84CPB2878; 85CPB1975).



Ester-stabilized azomethine ylides **91** bearing an ester moiety as the only C substituent cycloadd to methyl arylates to furnish two regioisomeric cycloadducts **182** (84TL1579; 85JOC2309; 86CL973; 87BCJ4067). N-Unsubstituted azomethine ylides **47** ($R^1 = \text{Ar}$, $R^2 = \text{H}$) derived from a thermal equilibration of the imines of α -amino esters are also reactive to acrylic olefins; this reactivity remains high enough to give cycloadducts **183**, even when the α position is substituted ($R^2 = \text{Ph}$ or Me) (78CC109; 80TL2461; 86CL1271). Cyano-stabilized analogs **49** ($R^1 = \text{Ph}$ or Et , $R^2 = \text{H}$ or Ph) react with methyl acrylate to produce **184** (86BCJ1809). In the cycloadditions of ylides **47** and **49**, the regio- and stereoselectivity depend upon the α substituent R^2 , as discussed in Sections III,C and D.

Substitution of an aryl or an alkyl group on the olefinic carbon of acrylic olefins would probably, reduce the reactivity in 1,3-dipolar cycloadditions with azomethine ylides. Crotonates, cinnamates, methacrylates, etc. are such cases. If an ylide reacts with these olefins, it may be regarded as one of the most reactive azomethine ylides.

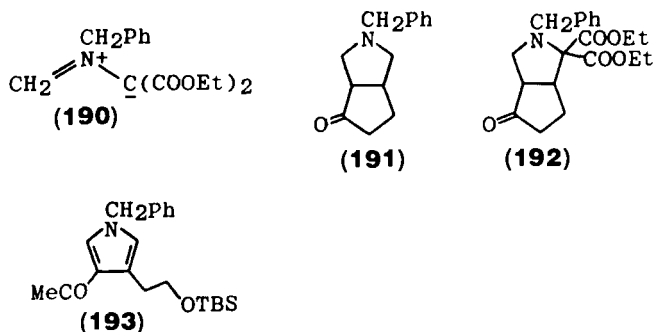
C-Phenyl-substituted ylide **32** ($R^1 = \text{Ph}$, $R^2 = \text{H}$), when generated from an N-benzylidenesilylmethylamine and water in HMPA, shows a high reactivity to methyl crotonate and methacrylate to produce regioselective cycloadducts **185** and **186** (84CL801; 86BCJ2537). Similarly, thioimide ylides **36** ($R^1 = \text{Ph}$ or alkyl, $R' = \text{Me}$) generated by the water-induced method, undergo very clean cycloadditions with acrylonitrile, methyl acrylate, crotonate, cinnamate, methacrylate, and 3-buten-2-one giving 1-pyrrolines **187** and **188** (85H2489; 87JOC2523). It is interesting that the same ylides (**36**) ($R^1 = \text{alkyl}$, $R' = \text{Me}$) are totally inert to these unsymmetrical olefins when generated from methyl triflate and N-silylmethylthioamides (86JOC1997).



Ester-stabilized azomethine ylides **79** ($R^1 = H$, $R^2 = Me$), generated by pyrolysis of the aziridine precursors, undergo cycloadditions to such sluggish olefins as *t*-butyl acrylate and (*E*)-6-silyloxy-3-hexen-2-one, whereas the (*Z*)-isomer of the latter showed no activity (85JOC2309). Ylide **43** ($R = PhCH_2$) and 3-ethoxy-2-butenal give the corresponding cycloadduct **189** (87JOC235).

As discussed in Section II,G, N-metallated azomethine ylides **124** ($M = Cu$), **128**, and **137** readily react with less reactive acrylic olefins, 3-buten-2-one, or acrolein to give regioselective cycloadducts **127**, **131**, and **138** (79S150; 80CC648; 82JCS(P1)1827; 86JCS(P1)1669). N-Lithiated azomethine ylides of ester-stabilized types **741** (88JOC(ip)), as well as cyano-stabilized types **144** (87BCJ3359), show a high reactivity to methyl acrylate, cinnamate, crotonate, and methacrylate to afford exclusively diastereoselective cycloadducts **142** and **145**. In the former ylides **144**, a variety of α,β -unsaturated ketones can be used successfully for ylide trapping. Extremely enhanced reactivity of **141** and **144** is indicated by the fact that the ylides α -substituted with an alkyl group still show a high reactivity toward such sluggish olefins.

Both a typical nonstabilized azomethine ylide **43** ($R = PhCH_2$) and a highly stabilized polar ylide **190** react with cyclopentanone to give **191** (85CPB2762) and **192** (84JCS(P1)2517).



Acetylenic dipolarophiles corresponding to acrylic olefins are propiolates or propynenitriles. Though the latter have found no application to the trapping of nonheteroaromatic azomethine ylides, the esters of acetylenecarboxylic acid, propiolates, have been very often employed in many examples. The nonstabilized azomethine ylides generated by the desilylation route (Section II,B) are very reactive to propiolates (81CL1213; 83CPB3939, 83JOC4773; 84CL2041, 84JOC3314; 85CPB2762, 85JOC4006; 86CB813; 87JOC235). The successful trapping of isolable ylide **151** (84H21) and acyl-stabilized ylide **76** ($R = H$, $EWG = C(=O)Ph$) with propiolate dipolarophiles is complementary to the above cases. In thermolyses of *N*-unsubstituted aziridines in the presence of propiolates, the Michael-type additions compete with the cycloadditions to the generated azomethine ylides (79CL1095; 82CJC2830).

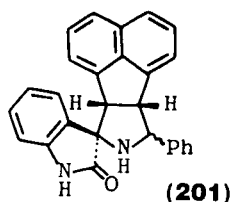
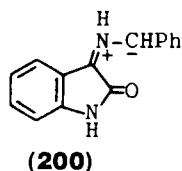
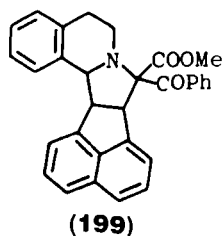
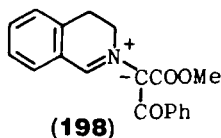
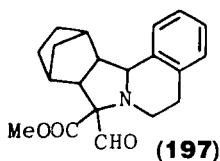
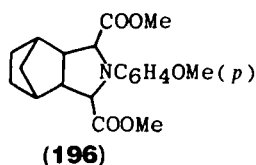
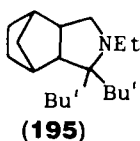
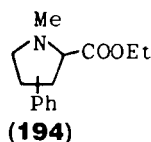
Use of activated acetylenes other than acetylenedicarboxylates and propiolates is quite rare. The following three examples are all that are known. 1,3-Diphenyl-1-oxopropyne (benzoylphenylacetylene) has been used to trap 3,4-dihydroisoquinolinium *p*-nitrobenzylide **76** ($R = H$, $EWG = p-NO_2C_6H_4$) (63TL1441) and diester-stabilized ylide **7** (66TL397). Ester-stabilized ylide **79** ($R^1 = H$, $R^2 = Me$, $R = PhCH_2$) undergoes a successful cycloaddition with 6-(*t*-butyldimethylsilyloxy)-2-oxo-3-hexyne to give pyrrole **193** after a spontaneous dehydrogenation (85JOC2309).

2. Nonactivated Olefins and Acetylenes

There are some examples known for the cycloaddition of azomethine ylides with nonactivated olefins such as aryl-substituted olefins, strained olefins, acyclic or cyclic olefins, and electron-rich olefins. Stabilized ylide **79** ($R^1 = H$, $R^2 = Et$, $R = Me$), bearing an ester moiety as the only C substituent, can be successfully trapped with styrene when generated by the deprotonation route (Section II,D) from ethyl sarcocinate and paraformaldehyde under reflux in toluene, to give **194** as a mixture of two regioisomers (86CL973).

Though the double bond of norbornene is so strained as to increase its reactivity, use of norbornene as an ylide-trapping olefin is quite rare. Nonstabilized azomethine ylide **73** is generated under strongly basic conditions that electron-deficient activated olefins cannot withstand and therefore undergo a base-induced polymerization. Norbornene is the only dipolarophile that has trapped **73** as a cycloadduct **195** (78JOC501). This makes an interesting contrast to the fact that two highly stabilized azomethine ylides, **7** and **151**, the latter being isolable, are readily captured by norbornene to

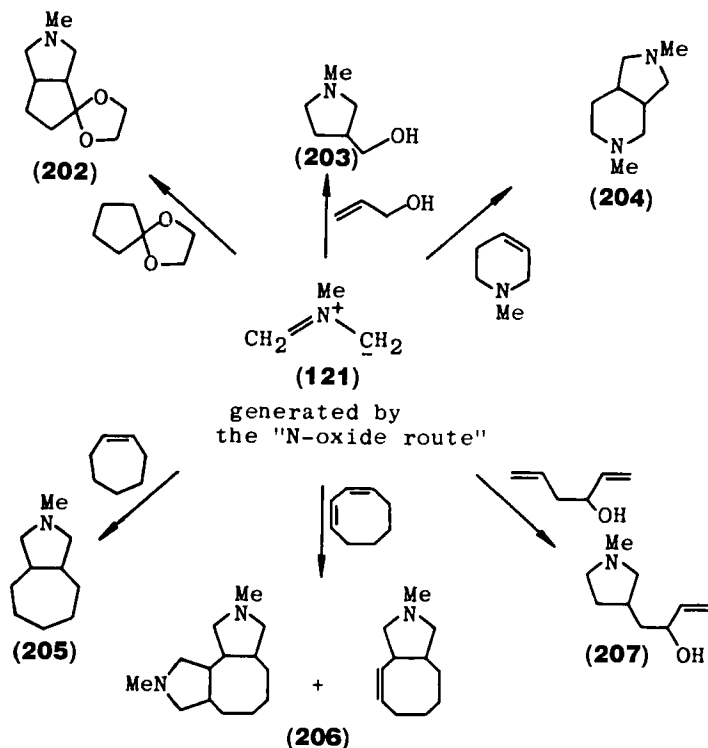
give the corresponding cycloadducts **196** and **197** (66TL397; 84H21). The reaction with the latter ylide (**151**) takes place in dichloromethane, though the reaction temperature was unspecified.



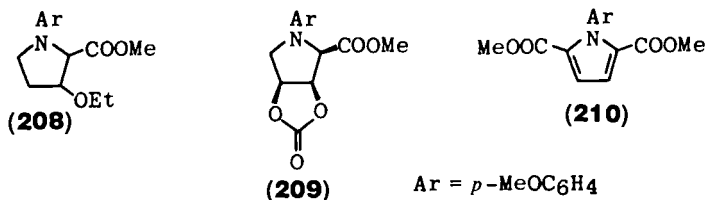
Acenaphthylene is expected to be poorer in reactivity with azomethine ylides than norbornene; examples are also quite limited. Isolable ylide **198**, obtained from 3,4-dihydroisoquinoline *N*-oxide and methyl phenylacet-
ylenecarboxylate via a sequence of cycloaddition and ring-opening reactions, is trapped with acenaphthylene at 70°C in benzene to produce **199** (84H21). Ylide **200**, generated by the decarboxylation route (Section II,E) using isatin and phenylglycine, reacts with acenaphthylene in boiling DMF for 10 min providing cycloadduct **201** as a single stereoisomer (84CC180).

As discussed in Section II,F, nonstabilized azomethine ylides **121**–**123** generated from the corresponding *N*-oxides and strong bases exhibit unusually high reactivity toward a variety of nonactivated olefins (83CC31; 85H653, 85CJC725, 85JOC2910). Involved are aryl-substituted olefins (*cis*- or *trans*-stilbene and styrene), terminal olefins (ethylene, 1-heptene, and allyl alcohol), cyclic olefins (cyclopentene, cycloheptene, cyclooctene, 1-cyclopentenone ethylene ketal, 1-methyl-1,2,5,6-tetrahydropyridine), 1,2-disubstituted (*E*)-olefins [(*E*)-1,1,4,4-tetramethoxy-2-butene], and the electron-rich olefin [(*E*)- β -methoxystyrene]. Though the same ylide (**121**) is accessible by the desilylation (Section II,B) and decarboxylation (Section II,E) routes, the ylides generated by these methods cannot be unusually reactive. As Roussi suggests,

the active species in the N-oxide case is probably a radical (83CC31). This point is very important to the understanding and even the control of the reactivity of azomethine ylide 1,3-dipoles. No evidence is now available as to how these particular azomethine ylides have come to possess radical-like properties. The high reactivity of ylide **121** is further demonstrated by its cycloadditions to conjugated or separated dienes, such as 1,3-cyclooctadiene, (*E,E*)-1,4-diphenyl-1,3-butadiene, 1,5-hexadiene, and 3-hydroxy-1,5-hexadiene (85CJC725). Some examples of cycloaddition of ylide **121** are shown with cycloadducts **202–207**.



Vinyl ethers classified as electron-rich olefins are expected to undergo cycloadditions with azomethine ylides activated by electron-withdrawing substituent(s) under the control of HOMO (dipolarophile) and LUMO (1,3-dipole) interaction (71TL2717; 73JA7287, 73JA7301). However, there are few known reactions in this category. Azomethine ylide **79** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R} = p\text{-MeOC}_6\text{H}_4$) of the ester-stabilized type can be trapped with ethyl vinyl ether or with the more electron-rich vinylene carbonate to give **208** or **209** (85JOC2309, 85TL3747). However, this highly reactive ylide (**79**) has failed to react with styrene, allyl alcohol, and cyclohexene. The authors



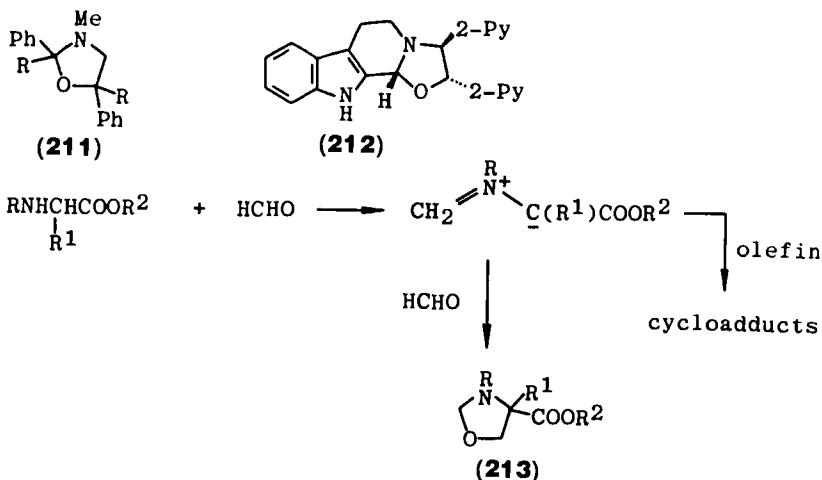
say that the olefins lacking electron-withdrawing or -donating substituents should be the least reactive dipolarophiles.

We have too little information to understand the reactivity of azomethine ylides toward nonactivated acetylenes since acetylenes bearing no electron-withdrawing substituent(s) have rarely been utilized in cycloaddition trapping of azomethine ylides. To the best of our knowledge, the only example is the reaction of azomethine ylide **7**, stabilized by two ester moieties, with acetylene itself in acetone at 125°C, producing pyrrole **210** after dehydrogenation with chloranil (66TL397).

3. Carbonyl Compounds and Imines

As already discussed (Section II,E), sarcosine undergoes a condensation with acetophenone or benzophenone to generate the corresponding azomethine ylide **98** (*R* = H or Ph), which is then trapped with the carbonyl compound giving rise to 3-methyl-2,5-diphenyl- or 3-methyl-2,2,5,5-tetra-phenyloxazolidine **211** (*R* = H or Ph) (70JOC2069). Similar condensation of 1,2,3,4-tetrahydroisoquinoline or tetrahydro- β -carboline with 2 equivalents of pyridine-2-carbaldehyde provides the stereoselective aldehyde cycloadduct **165** or **212** (86CC602). In these cases, the carbonyl compound serves both as the agent for ylide generation and as dipolarophile. As the 5-oxazolidinone **102** (*R* = trityl) is isolated as an ylide precursor in the reaction of *N*-tritylglycine with formaldehyde, the C-unsubstituted ylide **43** (*R* = trityl), generated by the thermolysis of **102**, can be utilized in cycloadditions with other aldehydes (87BCJ4079). The azomethine ylides, generated through the deprotonation route (Section II,D) using *N*-substituted α -amino esters and paraformaldehyde, undergo cycloadditions to formaldehyde to give oxazolidine-4-carboxylates **213** (87TL2973, 87TL2975).

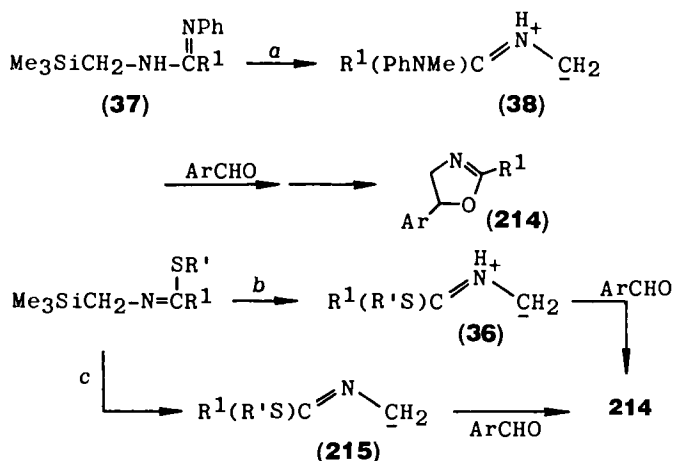
The above examples involve the *in situ* generation of azomethine ylides by condensation using carbonyl compounds. If no dipolarophile is present, the ylides generated attack the carbonyl compound to give oxazolidine derivatives. However, in most cases when an olefinic dipolarophile is present, these ylides can be trapped by the olefin. The olefins with a moderate activity will serve adequately for this purpose, for example, acrylates (85CC1566, 85TL2775; 86CL1271; 87BCJ4079) or even an inert olefin such as styrene



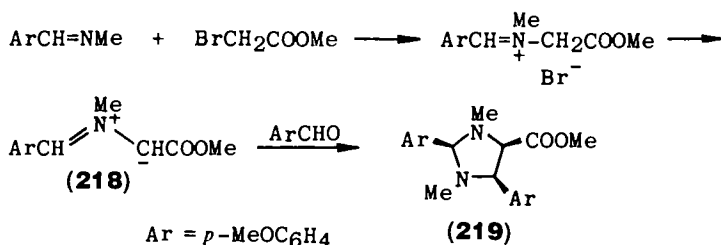
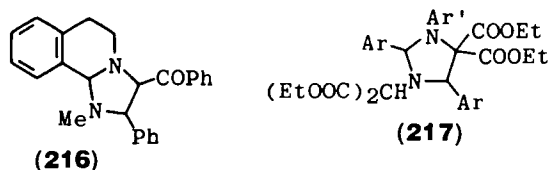
(86CL973; 87BCJ4079). In other words, the competitive ylide trappings in general favor olefinic dipolarophiles rather than carbonyl dipolarophiles, indicating that olefins would be better dipolarophiles toward azomethine ylides. Padwa has established a more quantitative estimate of the relative reactivity of C-unsubstituted azomethine ylide **43** ($\text{R} = \text{PhCH}_2$) toward a variety of dipolarophiles (87JOC235). Reactivities relative to that of benzaldehyde (1.0) are shown in parentheses: benzaldehyde is less reactive than thiobenzophenone (1.2), dimethyl fumarate (1.9), and *N*-phenylmaleimide (2.3), but more reactive than 1,1-bis(*p*-tolylsulfonyl)ethene (0.74). Two more examples for the reaction of ylide **43** with benzaldehyde are known (85T3529; 86CB813).

Azomethine ylides **38** generated from *N*-silylmethyl-*N'*-phenylamidines **37** show high reactivity toward a variety of aromatic aldehydes to produce 2-oxazolines **214** by a sequence of cycloaddition and spontaneous elimination of *N*-methylaniline (86JOC1997). By contrast, related ylides **36**, generated by the action of water on *N*-silylmethylthioimidates, are totally inert to carbonyl compounds (87JOC2523). Instead, on treatment with a fluoride anion, the thioimidates generate 2-azaallyl anion intermediates **215**, which are highly reactive to aromatic aldehydes and produce 2-oxazolines **214**.

Although imines were first employed in cycloadditions with azomethine ylides as early as 1963, there is only a limited number of reports concerning the imine cycloadditions. The first example is the reaction of acylstabilized **76** ($\text{R} = \text{H}$, $\text{EWG} = \text{COPh}$) with *N*-benzylidenemethylamine leading to cycloadduct **216** (63TL1441). Less stabilized ylide **3**, generated by a thermolysis of methyl 1-phenylaziridine-2-carboxylate, has also succeeded in the trapping by the same imine (66TL397).



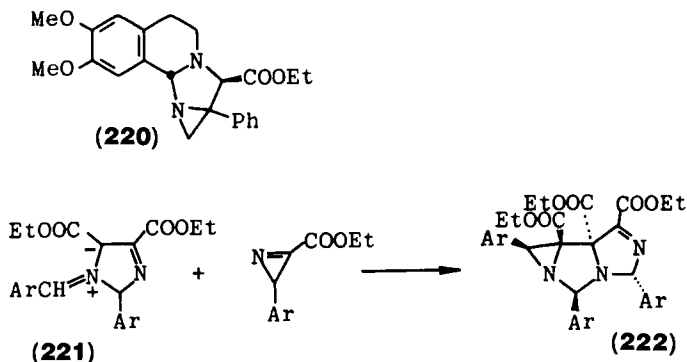
a : MeOTf in MeCN, rt. \rightarrow CsF b : H₂O in HMPA or DMF
 c : TBAF in THF, rt.



It would not be imprudent to say that most imine cycloadditions have been discovered unexpectedly during investigations on the generation of azomethine ylides. As already discussed (Section II,C), imines **60**, formed by the condensations of diethyl aminomalonate with aromatic aldehydes, quickly isomerize into highly stabilized azomethine ylides **61**, which are all trapped by the imine **60** to give imidazolidine derivatives **217** (80TL2197). It has also been described above (Section II,E) that the iminium salt **75** (R = OMe, EWG = CN), formed in the N-alkylation of 6,7-dimethoxy-3,4-dihydroisoquinoline with chloroacetonitrile, quickly loses a proton generating stabilized

ylide **76** ($R = \text{OMe}$, $\text{EWG} = \text{CN}$), which then undergoes a smooth cycloaddition with the isoquinoline giving **74** (82LA924). A similar example is the reaction of methyl bromoacetate with *N*-(*p*-methoxy)benzylidenemethylamine, which again involves a quick ylide generation and subsequent cycloaddition of the resulting ylide **218** with the imine leading to stereoselective cycloadduct **219** (82LA2146).

Ester-stabilized azomethine ylides **76** ($R = \text{MeO}$, $\text{EWG} = \text{COOR}'$) show a high reactivity to imines such as 2-phenyl-1-azirine and *N*-benzylidenemethylamine, cycloadduct **220** being obtained in the former case (82LA2146).



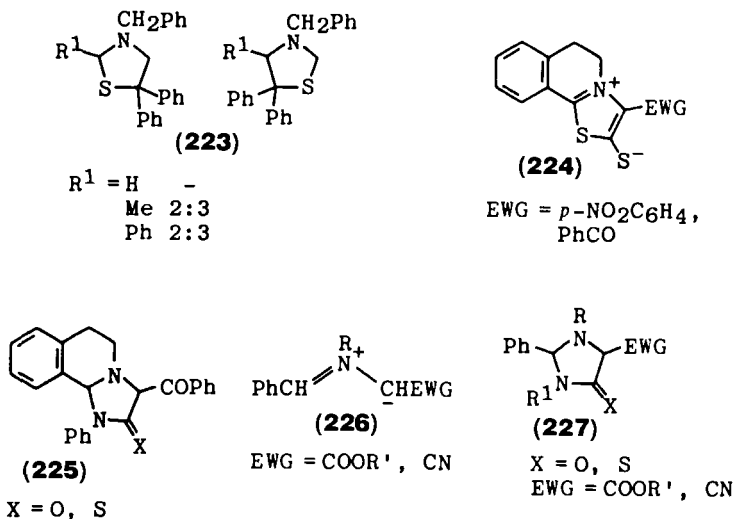
Azomethine ylides **221** of the ester-stabilized type can be generated by ring opening of the corresponding ring-fused aziridines and can cycloadd to 2-aryl-1-azirines in a stereoselective manner to give **222** (86JCS(P1)1119).

4. Other Carbon-Hetero Double Bonds

There are very limited examples for the trapping of azomethine ylide 1,3-dipoles by the dipolarophiles carrying a carbon-hetero double bond, other than carbon-oxygen and carbon-nitrogen. So it is difficult to state the differences of reactivity of different types of azomethine ylides toward these special dipolarophiles. The known examples are presented below.

Only one example is known for the azomethine ylide trapping with thio-carbonyl dipolarophiles. Nonstabilized azomethine ylides **41** ($R = \text{PhCH}_2$) undergo smooth cycloadditions in acetonitrile at room temperature with thiobenzophenone to give a mixture of two regioisomeric cycloadducts **223**, whose ratio is independent of the C substituent R^1 (87JOC235). Direct competition experiments using ylides **41** indicate that thiobenzophenone dipolarophile is more reactive than benzaldehyde but less than dimethyl fumarate.

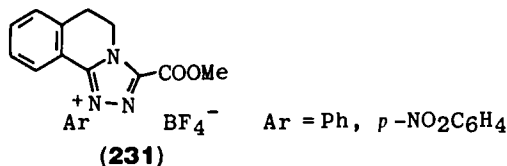
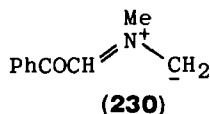
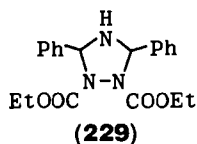
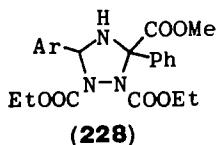
As early as 1963, interesting cycloadditions of 3,4-dihydroisoquinolinium methylides **76** ($R = H$, $\text{EWG} = p\text{-NO}_2\text{C}_6\text{H}_4$ or PhCO) with carbon disulfide were reported (63TL1441). A spontaneous dehydrogenation of the initial cycloadducts gives rise to red-colored thiazole-type mesoionic compounds **224**.



Ylide **76** ($R = H$, $\text{EWG} = \text{PhCO}$) cycloadds to the carbon–nitrogen double bond of phenyl isocyanate or isothiocyanate to produce fused 4-imidazolidinone (**225**, $X = O$) or 4-imidazolidinethione skeletons (**225**, $X = S$), respectively (63TL1441). Ester-stabilized azomethine ylides **226** ($\text{EWG} = \text{COOR}'$ and CN) show a similarly high reactivity toward these heterocumulenes, regioselective cycloadducts **227** being obtained in good yields (78T1153; 86T2283).

5. Nitrogen–Nitrogen Multiple Bonds

Although only limited examples are known, the electron-deficient nitrogen–nitrogen double bond of azodicarboxylates is also reactive to azomethine ylides. Thus, N-unsubstituted ylides **47** ($R^1 = \text{Ar}$, $R^2 = \text{Ph}$) and **108** ($R = \text{Ph}$), both generated through the tautomerization route (Section II,C), are captured as triazolidine cycloadducts **228** and **229**, respectively, with diethyl azodicarboxylate (77CC125; 78CC109). The former cycloadducts **228** are single stereoisomers, but their stereostructures are unspecified. Acyl-stabilized azomethine ylide **230**, generated by the decarboxylation route (Section II,E), is similarly trapped by the same azo compound (84CC182).



Surprisingly, isolable azomethine ylide **151** reacts with aryldiazonium tetrafluoroborates, at -30°C in acetonitrile, to produce fused triazolium salts **231** after the elimination of the formyl moiety from the initial cycloadducts (84TL65).

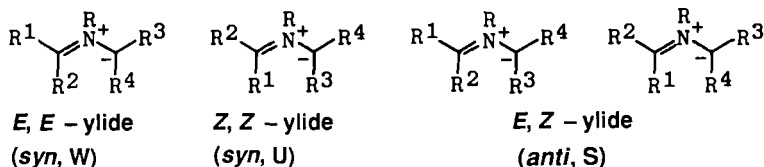
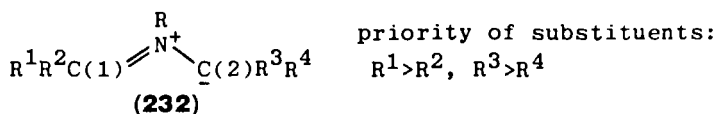
B. GEOMETRY OF YLIDES

As azomethine ylide 1,3-dipoles are usually transient intermediates, direct structural investigation is impossible. Accordingly, structures are derived from a consideration of their stable and isolable derivatives through a stereospecific process. Ylide structures are determined on the basis of structural analysis of their derivatives. Cycloaddition reactions are the most reliable ways to make derivatives because they usually take place stereospecifically with respect to both azomethine ylides and dipolarophiles.

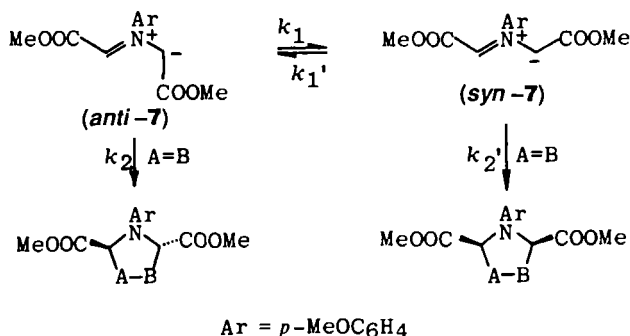
There are four geometries possible for unsymmetrically substituted azomethine ylides. Let us imagine an azomethine ylide **232** with a general substitution pattern of $\text{R}^1\text{R}^2\text{C}(1)=\text{NR}^+-\text{C}^-(2)\text{R}^3\text{R}^4$ and suppose that the substituents R^1 and R^3 are each of higher priority than the other substituent on the same carbon, R^2 or R^4 , respectively. The four geometries consist of one **W** shaped [(*E,E*)-dipole], one **U** shaped [(*Z,Z*)-dipole], and two **S** shaped configurations [(*E,Z*)-dipoles]. When both R^2 and R^4 are hydrogen, the (*E,E*)- and (*Z,Z*)-isomers refer to *syn*- or *cis*-azomethine ylides; the (*E,Z*)-isomers as *anti*- or *trans*-ylides.

1. Ylides from the Aziridine Route

As discussed briefly in Section II,A, dimethyl 1-(*p*-methoxyphenyl)aziridine-2,3-dicarboxylate (**6**) undergoes a stereospecific ring opening generating ester-

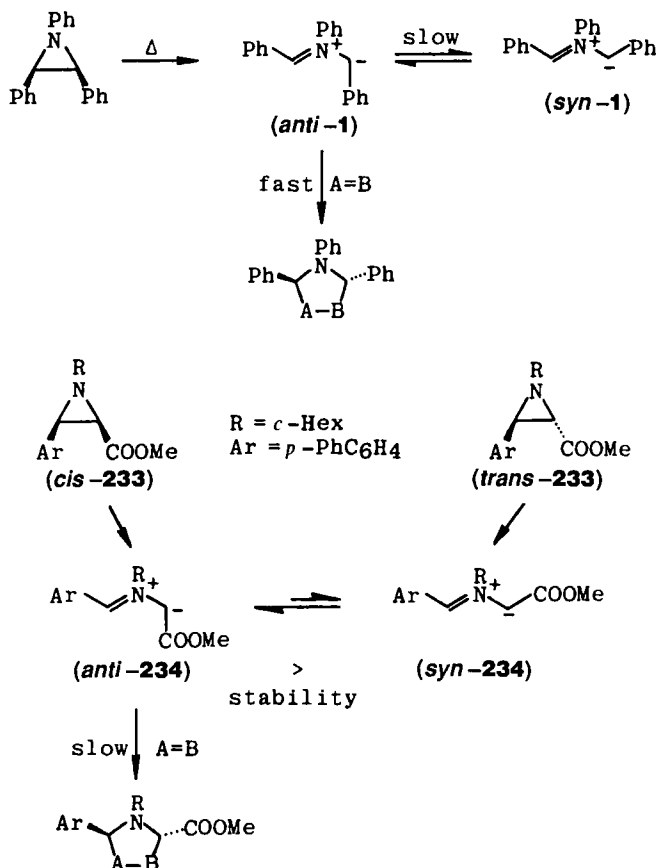


stabilized azomethine ylide **7**. Thermal opening of *cis*-**6** and *trans*-**6** leads to *anti*-**7** and *syn*-**7**, respectively, and photochemical opening of *cis*-**6** and *trans*-**6** gives rise to *syn*-**7** and *anti*-**7**, respectively (67JA1753). As *anti*-**7** and *syn*-**7** can interconvert to each other (rates: k_1 and k'_1 and k'_1), the kinetic azomethine ylides can be trapped (rates: k_2 and k'_2) only with a highly reactive dipolarophile such as dimethyl acetylenedicarboxylate. On the basis of the energy profile estimated for the above ring opening of aziridine **6** and the isomerization between the two isomeric dipoles **7** (71JA1779), the geometry of the reacting azomethine ylides **7** may be determined from relative rate constants k_1/k_2 or k'_1/k'_2 involving the ylide isomerization (between *anti*-**7** and *syn*-**7**) and the cycloaddition trapping of **7**. In general, reaction rates both for the dipole isomerization and cycloaddition trapping depend upon the substitution pattern of azomethine ylides and upon the reactivity of the particular dipolarophile used for the trapping.

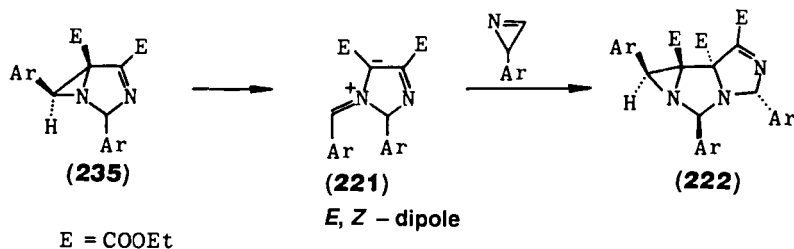


Thermolysis of *cis*-1,2,3-triphenylaziridine in boiling toluene in the presence of a variety of olefinic trapping agents, such as maleates, fumarates, (*E*)-1,2-dibenzoyl ethene, and maleic anhydride, has afforded the corresponding pyrrolidine derivatives bearing 2,5-*trans*-phenyl substituents, indicating that the isomerization of *anti*-ylide **1** into the *syn*-isomer is sufficiently slower than ylide trapping with these olefins (71CC1187). On the other hand, a quick

isomerization of *syn*-azomethine ylide *syn*-**234** to thermodynamically more stable *anti*-isomer *anti*-**234** has been observed in the thermolysis of both methyl *cis*- and *trans*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylates **233**. The cycloadducts obtained by ylide trapping using maleimides, maleates, and fumarates are mostly 2,5-*trans*-pyrrolidines, regardless of the stereochemistry of the starting aziridines (70JOC888). Even dimethyl acetylenedicarboxylate cannot suppress the ylide isomerization. Another example of quick ylide isomerization is known (79JOC255).



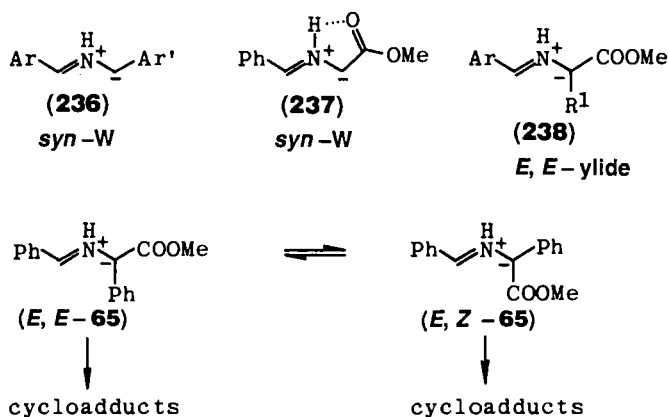
A ring-fused aziridine system **235** in which Ar and the ester group are *cis*, undergoes a stereospecific conrotatory ring opening leading to (*E,Z*)-azomethine ylide **221**, which is trapped with an azirine in a stereo- and face-selective, and stereospecific fashion providing tricyclic product **222** (86JCS(P1)1119).



2. Ylides from the Tautomerization Route

In the generation of azomethine ylides by the tautomerization route (Section II,C), the acidic α hydrogen of imines, mostly bearing an ylide-stabilizing α substituent of the carbonyl type, migrates onto the imine nitrogen leading to N-unsubstituted azomethine ylides. As the nitrogen is unsubstituted, the outer side of the ylide triangle is sterically less congested so that the **W**-shaped *syn* geometry is the sterically most favorable configuration for these types of ylides. Thus, 1,3-diaryl-substituted azomethine ylides **236** have been captured as (*E,E*)-isomers in cycloadditions (77CC768; 83TL4363).

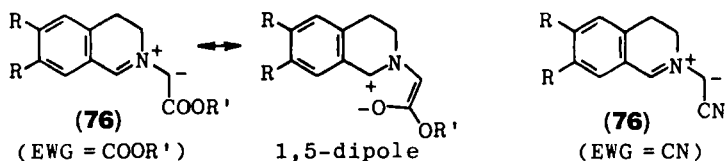
Another stabilization of the **W**-shaped *syn*-geometry is added when N-unsubstituted azomethine ylides carry an ylide-stabilizing substituent of the carbonyl type. The **W**-shaped geometry may be stabilized by a hydrogen bond between the NH and the carbonyl oxygen. The azomethine ylide **237** generated by a thermal tautomerization of methyl *N*-benzylideneglycinate has been trapped by dimethyl maleate and fumarate exclusively as a *syn*-ylide (78TL2885). Introduction of an alkyl group at the α position of the imines of α -amino esters does not collapse the highly stabilized (*E,E*)-configuration (**238**), even if the alkyl group R^1 is a sterically crowded isopropyl moiety (78CC109; 83TL4363, 83TL4457; 84JCS(P1)41). In the case of α -substitution with an aryl moiety, for example, imines of phenylglycine, the hydrogen bond-stabilized (*E,E*)-geometry (*E,E*)-**65** participates in the cycloaddition with highly reactive dipolarophiles, such as dimethyl acetylenedicarboxylate, *N*-phenylmaleimide, maleic anhydride, and methyl propiolate (78CC109; 82CC384; 83TL1201; 85T3547). However, when ylide trappings are made with relatively sluggish olefins, such as dimethyl maleate and methyl acrylate, both (*E,E*)-**65** and (*E,Z*)-**65** are involved in the cycloadditions (80TL2461). Grigg, who greatly contributed to the azomethine ylide chemistry with his discovery of the tautomerization route (Section II,C), explains that the kinetically generated (*E,E*)-ylide gradually isomerizes to the (*E,Z*)-ylide [*(E,E*)-**65** \rightarrow (*E,Z*)-**65**], and that this isomerization is facilitated by the α -phenyl substitution.



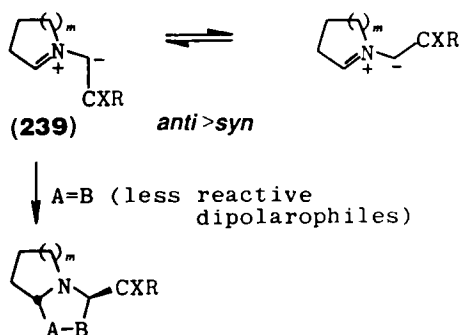
3. Ylides from the Deprotonation Route

α -Deprotonation of the iminium salts derived from secondary amines and aldehydes leads to N-substituted azomethine ylides (Section II,D). The difference between N-unsubstituted and N-substituted azomethine ylides of carbonyl-stabilized types is that no ylide stabilization by a hydrogen bond exists in the latter case. The N-substitution brings about the exclusive participation of *anti*-ylides [(*E,Z*)-forms] in their trapping reactions using a variety of active to sluggish olefinic dipolarophiles (86CL1271; 87BCJ4067). The selective participation of the *anti*-ylides can be explained by dipole stabilization through a proximate interaction of both termini of the extended dipole, 1,5-dipoles (85CL355, 85BCJ3137).

3,4-Dihydroisoquinolinium methylides of ester-stabilized types **76** (EWG = COOR'), generated by the deprotonation route of the corresponding iminium salts, undergo stereospecific cycloadditions of the *anti*-ylides to imines (82LA924, 82LA2146) and olefins (83JCS(P1)1961, 83T369). This exclusive contribution of the *anti*-ylides is consistent with the above 1,5-dipole stabilization. However, the *anti*-ylide-specific cycloaddition of a cyano-stabilized analog **76** (EWG = CN) to an imine (82LA924) cannot be explained on the same basis.



The deprotonation route, using cyclic secondary amines and the carbonyl compounds that are activated by the adjacent carbonyl or related groups, generates azomethine ylides of carbonyl-stabilized or related types **239** (86CC602). These ylides are trapped exclusively as *anti* forms with *N*-methylmaleimide, a highly reactive dipolarophile. Interesting is the observation that the ylide isomers participating in the cycloadditions to the less reactive methyl acrylate and pyridine-2-carbaldehyde are again selectively *anti*-ylides. This might indicate that *anti* geometry has higher stability than *syn* geometry when the ylide nitrogen is substituted.

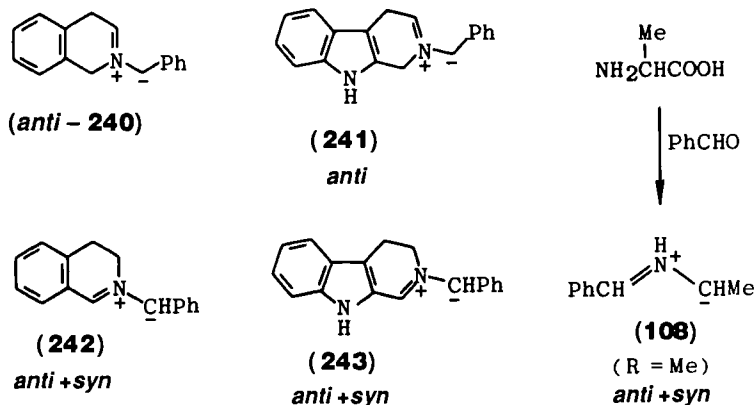


4. Ylides from the Decarboxylation Route

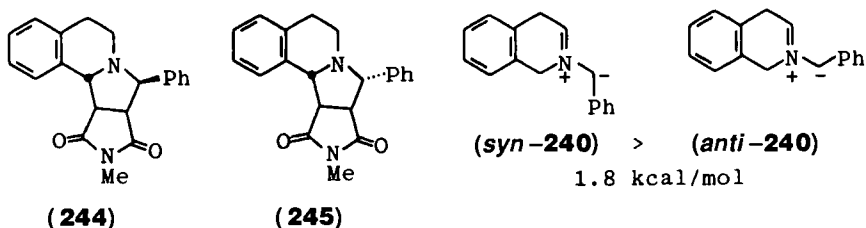
Decarboxylative condensations of *N*-substituted or *N*-unsubstituted α -amino acids with carbonyl compounds offer the most convenient generation of a wide variety of azomethine ylides (Section II,E). The intermediacy of 5-oxazolidinones is ascertained by the fact that in several cases 5-oxazolidinones have been actually isolated and their thermolysis leads to the generation of azomethine ylides (76CSR377; 77MI1; 87BCJ4079). As the decarboxylation of the 5-oxazolidinone intermediates would take place stereospecifically in a concerted manner, 2,4-*trans*- and 2,4-*cis*-isomers of the 5-oxazolidinones give rise to *anti*- and *syn*-azomethine ylides, respectively. Condensations of cyclic α -amino acids with aldehydes produce 2,4-*trans* bicyclic oxazolidinones as thermodynamically more stable products. Accordingly, the exclusive formation of *anti*-ylides is expected in the decarboxylation route (Section II,E).

This expectation has been realized in many cases involving the condensation of aldehydes with cyclic α -amino acids, such as proline, pipercoline, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydro- β -carboline-2-carboxylic acid, and thiazoline-4-carboxylic acid (87CC47). The ylides generated by this route are trapped as the cycloadducts of *anti*-ylides, for example **111**, **112**, **116**, *anti*-**240**, and **241**, in cycloadditions using maleimides.

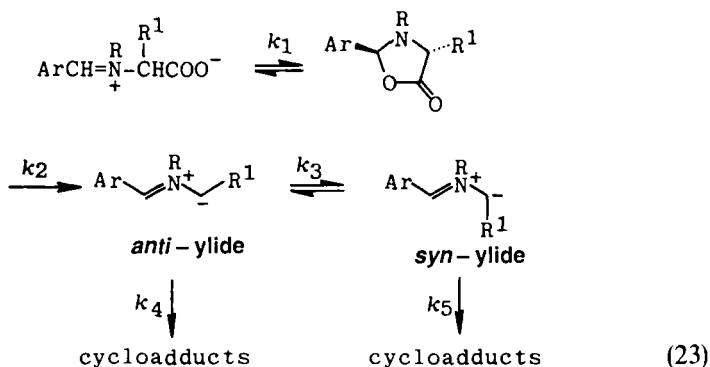
Contrary to these high stereoselective *anti*-ylide generations, similar ylide generated by this route are trapped as the cycloadducts of *anti*-ylides, for tetrahydro- β -carboline-4-carboxylic acid, and alanine give mixtures of the maleimide cycloadducts derived from *anti*- and *syn*-ylides **108**, **242**, **243** (84CC180; 87CC47). This difference in ylide stabilization has not been well interpreted.



The dipole stereochemistry is sensitive to both structural change in the α -amino acids and aldehydes, and reaction temperature (87CC49). The reaction of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid with benzaldehyde and *N*-methylmaleimide gives a 1:1 mixture of the maleimide cycloadducts **244** and **245** of *anti*- and *syn*-dipoles **242** at 120°C in DMF (1 hr), and a 2.7:1 mixture at 21°C in the same solvent (120 hr). Because MNDO calculations on the related *anti*- and *syn*-ylides **240** show that *syn*-**240** is 1.8 kcal/mol more stable than *anti*-**240**, the preference of the *anti*-ylide cycloadducts **245** must be a kinetic result.



In the end, the stereochemistry of the reacting dipole is determined by the relative rates of the reversible ring closure of the iminium carboxylate betaine into 2,4-*trans*-5-oxazolidines (k_1), the decarboxylative ylide generation (k_2), the isomerization of *anti*-ylides into *syn*-ylides (k_3), and cycloaddition trapings (k_4 and k_5), as shown in Eq. (23).

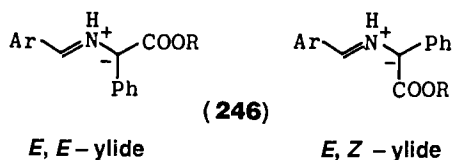


5. Ylides from the *N*-Metallation Route

The first generation example of *N*-metallated azomethine ylides includes the deprotonation of structurally rigid *N*-pyruvylideneglycinatocopper(II) (**124**) (79S150). In this case, exclusive generation of metal-chelated (*E,E*)-azomethine ylide **126** must be involved. However, its regioselective cycloadditions with a variety of symmetrical and unsymmetrical olefin dipolarophiles have produced a mixture of stereoisomeric cycloadducts, after the demetallation procedure (80CC648). Later it was demonstrated that this reduced (*E,E*)-specificity is due to partial epimerization during cycloaddition in the presence of base or the demetallation step. The stereochemical integrity of the metal-chelated (*E,E*)-ylides has been proved in many cases in which the metal-chelated azomethine ylides **128**, containing copper(II), zinc(II), cadmium(II), and lead(II), are stereospecifically trapped with a wide variety of olefin dipolarophiles (86JCS(P1)1669).

Palladium-chelated azomethine ylides **135** react exclusively as (*E,E*)-dipoles with *N*-phenylmaleimide to furnish stereoselective cycloadducts of chelated types **136** (86CC631).

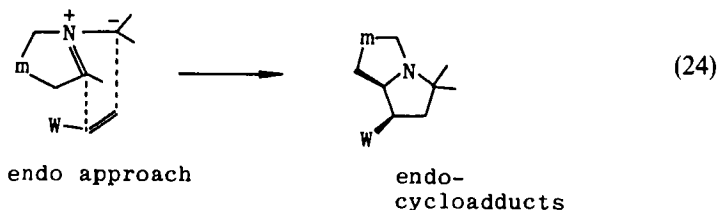
The cycloaddition of azomethine ylides generated from the imines of α -aminophenylacetate with an unreactive olefin such as methyl acrylate are very poor in stereospecificity with respect to ylide geometry, both (*E,E*)- and (*E,Z*)-azomethine ylides **246** being captured as cycloadducts (80TL2461). On the other hand, a similar reaction in the presence of a catalytic amount of sodium methoxide in benzene allows the exclusive participation of the single geometry [(*E,E*)-dipole] of dipoles **246** (80CC648). One closely related example has been reported. The imines of α -amino esters bearing an α substituent such as methyl or isopropyl are activated by the action of lithium bromide and triethylamine, and the resulting intermediates **141** undergo exclusively (*E,E*)-specific cycloadditions to a wide variety of olefin dipolarophiles to give **142** (88JOC1384).



Similarly, the imines of α -aminonitriles are activated by LDA as N-lithiated azomethine ylides **144**, which undergo smooth cycloadditions, even with inactive olefins at -78°C , to furnish 1-pyrrolines **145** (87BCJ3359). The ylide geometry with respect to the cyano-substituted carbon is not clear, since this carbon becomes an sp^2 hybrid through the elimination of lithium cyanide after cycloaddition. However, selective construction of 4,5-cis stereochemistry in the cycloadducts **145** is important in organic synthesis.

C. STEREOSELECTIVITY

Almost all cycloadditions of azomethine ylides with olefin dipolarophiles proceed in a stereospecific manner with respect to both the ylides and the dipolarophiles. In other words, the stereochemistry of the starting ylides and olefins is retained in the cycloadducts. The geometry of the reacting azomethine ylides has been discussed in the preceding section (Section III,B). The stereostructures of the cycloadducts formed in cycloadditions of azomethine ylides with olefinic dipolarophiles are determined by the approach of these two planar molecules, whether endo or exo. In the endo transition state, the ylide molecules approach the olefinic molecules with the ylide triangle and the olefin-activating substituent overlapping [Eq. (24)]. The overlapping may be caused by an attractive interaction between the extended conjugation of the dipolarophile and the dipole. This attractive interaction overwhelms the repulsive interaction of these two molecules.



The terms endo and exo have long been used to represent the stereochemical pathway of the HOMO(dipole)–LUMO (dipolarophile) interaction-controlled cycloadditions. However, on the basis of the stereochemical analysis of the cycloadducts alone, the approach (endo or exo) cannot be specified. There are two geometries possible for each of the *anti*- and *syn*-

ylides. In the case of *syn*-ylides, the endo and exo approaches lead to *cis*- and *trans*-cycloadducts, respectively, since **W**-shaped dipoles are generally much more stable than **U**-shaped ylides. However, identification of the reacting dipoles is quite difficult in the cycloadditions of some *anti*-ylides, so that the *cis* and *trans* structures of cycloadducts are not directly related with endo and exo approaches. Such a complication can also occur when (*E*)-olefins are employed.

The origin of the endo attractive interaction has not been clearly understood, as briefly mentioned above. There are some likely explanations based upon secondary orbital overlapping interactions involving the substituents of dipoles and dipolarophiles (83T369; 86CL1113). In this context, the terms endo and exo are used only when the ylide geometries are definitely confirmed and the authors are certain that their usage would not confuse the readers. It would be convenient to use the same terms for the stereochemical description of other cycloadditions using electron-rich, aryl-activated, and alkyl-substituted olefin dipolarophiles.

1. Cycloadditions to Cyclic *cis*-Olefins

Maleimides and maleic anhydride have been most frequently employed as cyclic *cis*-olefin dipolarophiles in the stereochemical investigation of 1,3-dipolar cycloadditions, especially on the endo and exo selection of the reaction. They are one of the most reactive dipolarophiles toward many kinds of azomethine ylide 1,3-dipoles. Because of their structural simplicity, the only stereochemical variation possible in cycloadditions is an endo and exo selection. If a strong attractive interaction exists between the extended conjugation of these dipolarophiles and azomethine ylides, an endo-selective cycloaddition results.

Table VIII summarizes the cycloaddition reactions of azomethine ylides with maleimides and maleic anhydrides. The upper part of the table involves endo-selective cycloadditions and the lower part nonselective reactions. Endo selectivity is closely related to the substitution pattern of the azomethine ylides used. The azomethine ylides that show high endo selectivity to these cyclic olefins bear an ylide-stabilizing substituent of the carbonyl or cyano type (EWG) at one carbon and an aryl, heteroaryl, acyl, or 1-alkenyl substituent (R^1) at the other. These key substituents must be present for high endo selectivity, although the substituent (*R*) on the ylide nitrogen is equally important.

Importantly, the azomethine ylides that show high endo selectivity are all N-unsubstituted or N-metallated, and they are mostly generated by the tautomerization (Section II,C) or the N-metallation (Section II,G) route. These

TABLE VIII
 endo-SELECTIVE CYCLOADDITIONS OF AZOMETHINE YLIDES TO MALEIMIDES OR MALEIC ANHYDRIDE^a
 $R^1CH=NR^+ - C(R^2)^- EWG + \text{maleimides or maleic anhydride} \rightarrow \text{endo-cycloadducts } \mathbf{247}$ (see **247** on p. 326)

X	R ¹	EWG	R ²	R	Reference
O	Ph	COOMe	Ph, PhCH ₂ SCH ₂ , 3-InCH ₂	H	78CC109
O	2-Thienyl	COOMe	Ph	H	78CC109
NH	COOH	COOH	Me	Cu	86JCS(P1)1669
NMe	Ph	COOMe	H	H	86CL1271; 87BCJ4067
NMe	PhCO	COOMe	H	H	86CL1271; 87BCJ4067
NMe	<i>i</i> -Pr	COOMe	H	H	86CL1271; 87BCJ4067
NMe		RR ² = 2-(CH ₂) ₂ -3-indolyl, EWG = COOEt		—	86CC602
NMe ^b	Ph	CN	H	H	85CL1601; 86BCJ1809
NMe ^b	PhCO	CN	H	H	86BCJ1809
NMe ^c	PhCH=CMe(<i>E</i>)	CN	Ph	H	86BCJ1809
NMe ^c	Et	CN	Ph	H	86BCJ1809
NPh	<i>p</i> -R'C ₆ H ₄ ^d	COOMe	Ph	H	82CC384; 83TL4457; 83TL4457
NPh	<i>o</i> -R'C ₆ H ₄ ^e	COOMe	Ph	H	83TL4457
NPh	R ¹ = 2-Pd-4-R'C ₆ H ₃ , ^f	EWG = COOMe, R ² = H, Me, PhCH ₂ , <i>i</i> -Bu, Ph		Pd	86CC631
NPh	Ph	COOMe	PhCH ₂ , PhCH ₂ SCH ₂	H	78CC109
NPh	2-Naphthyl	COOMe	1-Cyclopentenyl	H	82CC384
NPh	2-Thienyl	COOMe	Ph	H	78CC109
NPh	PhCH=CH(<i>E</i>)	COOMe	Ph	H	82CC384

NPh	$R^1 = \text{CH}_2=\text{CH}(\text{CH}_2)_m$ ($m = 3, 4$), EWG = COOMe, $R^2 = \text{Ph}$	H	85T3547
NPh	$R^1 = \text{CH}_2=\text{CHCH}_2\text{C}(\text{Me})_2$, EWG = COOMe, $R^2 = \text{Ph}$	H	85T3547
NPh	$R^1 = p\text{-MeOC}_6\text{H}_4$, Me, CH_2OH , 3-In CH_2 , $R^2\text{EWG} = o\text{-COC}_6\text{H}_4\text{CO}$	H	84CC180
NPh	$R^1 = o\text{-R}'\text{OC}_6\text{H}_4$, ^g EWG = COOH, $R^2 = \text{PhCH}_2$	H	83TL4457
NPh	$o\text{-HOC}_6\text{H}_4$ COOH CH_2OH , $\text{CH}_2\text{CH}_2\text{SMe}$, $(\text{CH}_2)_4\text{NH}_2$	H	83TL4457
NR' ^{b,h}	Ph CN H	H	85CL1601; 86BCJ1809
NPh	$R^1 = 3\text{-HO-5-HOCH}_2\text{-2-Me-4-Py}$, EWG = Ph, $R^2 = \text{H}$	H	84CC182
NPh	$R^1 = \text{EWG} = 3\text{-HO-5-HOCH}_2\text{-2-Me-4-Py}$, $R^2 = \text{H}$	H	83TL4363

^a Azomethine ylides that showed poor stereoselectivity to maleimides: $\text{PhCH}=\text{NH}^+-\text{C}^-(o\text{-COC}_6\text{H}_4\text{CO})$, (84CC180); $[(\text{CH}_2)_3\text{CH}=\text{N}^+]-\text{C}^-(o\text{-COC}_6\text{H}_4\text{CO})$, (84CC182); $\text{CH}_2=\text{NR}^+-\text{CH}^-\text{COOR}^2$ ($R = \text{Me, Ph}$), (85JOC2309; 86CL973); $R^1\text{CH}=\text{NR}^+-\text{CH}^-\text{COOR}^2$ [$R = \text{Me, Ph, } p\text{-MeOC}_6\text{H}_4$; $R^1 = \text{H, Ph, Et, MeCH}=\text{CH}(E)$], (86CL1271; 87BCJ4067); $\text{RCH}=\text{NH}^+-\text{C}(\text{CN})^-\text{Ph}$ [$R = \text{Ph, MeCH}=\text{CH}(E), \text{PhCH}=\text{CH}(E)$], (86BCJ1809); $\text{PhCH}=\text{NH}^+-\text{CH}_2^-$, (82CPB3167, 82TL2589; 84CL801; 85CPB1975; 86BCJ2537; 87BCJ4079); $\text{PhCH}=\text{N}(\text{Me})^+-\text{CH}_2^-$, (86CL973); $\text{ArCH}=\text{NH}^+-\text{CH}^-\text{R}$ [$\text{Ar} = \text{Ph, } p\text{-R}'\text{C}_6\text{H}_4$ ($R' = \text{NMe}_2, \text{OMe, CF}_3, \text{CN, NO}_2$); $R = \text{Ph, 2-Py, 2-(5-methyl)thiazolyl, Me, PhCH}_2, \text{MeSCH}_2\text{CH}_2, 2,6\text{-dimethyl-5-heptenyl}$], (83TL4363; 84CC180; 87CC47, 87CC49); $3\text{-PyCH}=\text{NH}^+-\text{C}^-[(\text{CH}_2)_m]$ ($m = 4, 5$), (84CC182); $[(\text{CH}_2)_m\text{CH}=\text{N}^+]-\text{CH}^-\text{2-Py}$ ($m = 3, 4$), (87CC49); $(\text{CH}_2\text{SCH}_2\text{CH}=\text{N}^+)-\text{CH}^-\text{Ar}$ ($\text{Ar} = \text{Ph, 2-Py}$), (87CC47); $[o\text{-(CH}_2)_2\text{C}_6\text{H}_4\text{CH}=\text{N}^+]-\text{CH}^-\text{Ar}$ ($\text{Ar} = \text{Ph, 2-Py}$), (87CC49); $[o\text{-CH}_2\text{C}_6\text{H}_4\text{CH}_2\text{CH}=\text{N}^+]-\text{CH}^-\text{Ar}$ ($\text{Ar} = \text{Ph, } p\text{-NO}_2\text{C}_6\text{H}_4, p\text{-NMe}_2\text{C}_6\text{H}_4$), (87CC47, 87CC49).

^b endo-Selective with respect to the carbon substituted by R^1 .

^c Isolated as 1-pyrrolines.

^d $R' = \text{H, NMe}_2, \text{OMe, CF}_3, \text{CN, NO}_2$.

^e $R' = \text{MeO, CH}_2=\text{C}(\text{Me})\text{CH}_2\text{O}$.

^f $R' = \text{H, } i\text{-Pr, NO}_2$.

^g $R' = \text{H, Me}$.

^h $R' = \text{Me, } p\text{-NO}_2\text{C}_6\text{H}_4$.

dipoles have an (*E,E*)-configuration, in which the electron-withdrawing group and the substituent R^1 on the other carbon are *syn*. In the transition state, and ylide triangle and/or the extended conjugation through the ylide substituents EWG and R^1 can positively overlap with the plane of dipolarophiles, presumably due to secondary orbital attraction. Therefore, the substituent R^2 may not bring about serious steric congestion in the endo transition state. This is why even the dipoles bearing a bulky substituent R^2 (e.g., Ph, PhCH_2 , 3-indolylmethyl, *i*-Bu) can be effectively involved in the endo-selective cycloadditions. When both substituents on the same ylide carbon, EWG (CN) and R^2 (H), are equally small in size, the other substituent R^1 is responsible for the endo selectivity. In such a case, the reacting dipole consists of two configurations, (*E,E*) and (*E,Z*)-geometries. However, the most bulky substituent, R^1 , is always outside of the triangle, and hence the high endo selectivity is achieved regardless of the stereochemistry on the other carbon.

It is interesting to compare the endo selectivities of two closely related types of dipoles. The ylides **47**, derived by an imine–azomethine ylide tautomerism of the imines of α -amino esters (Section II,C), are typical dipoles that exhibit high endo selectivity in cycloadditions to cyclic olefins. On the other hand, N-substituted derivatives **79**, derived by the deprotonation route (Section II,D) from N-substituted α -amino esters and aldehydes, are very poor in endo selectivity. The N-unsubstituted dipoles **47** are involved in the cycloadditions as (*E,E*)-ylides (or *syn*-ylides), while the N-substituted dipoles **79** as (*E,Z*)-ylidic forms (or *anti*-ylides). However, the difference in ylide geometry is not the only reason for the lowered endo selectivity of **79**, since the *anti* forms of heteroaromatic N-ylides undergo exclusive endo-selective cycloadditions with cyclic *cis*-olefins (83H1907; 84CL465; 85BCJ3137).

endo Selectivity of the azomethine ylides having a general structure of $R^1\text{CH}=\text{NR}^+-\text{CH}^-\text{COOR}^2$ has been investigated in cycloadditions with *N*-(*p*-tolyl)maleimide (86CL1271; 87BCJ4067). As described above, the reaction is 100% endo selective for several R^1 (Ph, PhCO , *i*-Pr), when R is hydrogen. The endo:exo ratios are dependent upon the substituent R on the nitrogen and independent of the substituent R^1 arising from aldehydes [78:22, 76:24, 77:23, 62:38 for $R^1 = \text{Ph}$, $\text{MeCH}=\text{CH}(\text{E})$, Et, H when R is methyl; 45:55, 47:53, 50:50 for $R^1 = \text{Ph}$, Et, H when R is phenyl]. These data indicate that the secondary orbital interaction between the dipolarophile and R^1 is not responsible for the endo selectivity. In the endo transition state, some steric repulsion should work between the plane of the dipolarophile and the ylide substituent R, and this is the primary factor lowering endo selectivity. When the rigid ring structure of maleimides and maleic anhydride is replaced by a flexible conjugation of maleates, such steric congestion is diminished, achieving an exclusive endo-selective cycloaddition even to the N-substituted azomethine ylide 1,3-dipoles as shown later.

N-Unsubstituted azomethine ylides bearing an aryl substituent on each

carbon undergo smooth cycloadditions to maleimides as (*E,E*)-dipoles, but in a nonstereoselective manner. Surprisingly, the pyridoxal-derived dipoles show an exclusively high endo selectivity (83TL4363; 84CC182).

2. Cycloadditions to Symmetrical Acyclic Olefins

Typical acyclic olefins of symmetrically substituted types are the esters of maleic and fumaric acids. Though maleimides and maleates are both symmetrical *cis*-olefins, these two exhibit quite different stereoselectivity in cycloadditions to azomethine ylides. There are relatively limited examples known for the stereoselective cycloadditions of azomethine ylides to symmetrical acyclic olefins. These stereoselective cycloadditions are listed in Table IX, and nonstereoselective reactions in Table X.

The azomethine ylides that exhibit high stereoselectivity to symmetrical acyclic olefins are again ester- or cyano-stabilized types, and also N-unsubstituted or N-metallated types. The only exception is the N-substituted ylides with a general formula $\text{ArCH}=\text{N}^+\text{R}''-\text{CH}^-\text{COOR}'$, whose poor endo selectivity to maleimides has been discussed above.

Selectivity in cycloadditions to maleates is mentioned first. The stereoselective cycloadducts produced in maleate cycloadditions are all 2,3-*cis*-pyrrolidines, indicating that the aryl or 1-alkenyl substituents as R^1 are overlapping with one of the maleate esters in the transition state. More azomethine ylides show high stereoselectivity to dimethyl maleate than to dimethyl fumarate. Thus, there are several azomethine ylide 1,3-dipoles in Table IX that show high stereoselectivity to maleate but poor to fumarate. The N-unsubstituted azomethine ylides $\text{RCH}=\text{NH}^+-\text{CH}^-\text{COOR}'$, derived from the imines of α -amino esters, are highly endo selective to maleimides, but poor in stereoselectivity to dimethyl maleate; on the contrary, the N-substituted derivatives $\text{RCH}=\text{NR}^+-\text{CH}^-\text{COOR}'$ are nonstereoselective to maleimides, but exclusively stereoselective to the maleate.

The azomethine ylides that undergo highly stereoselective cycloadditions to dimethyl fumarate are relatively limited. They bear an ylide-stabilizing substituent on one carbon and an aryl moiety on the other. Here again, high stereoselectivity of N-metallated dipoles is noted.

D. REGIOSELECTIVITY

In the cycloaddition reactions between both unsymmetrically substituted azomethine ylides and dipolarophiles, formation of two regioisomeric cycloadducts is possible. The regioselectivity depends upon the unsymmetrical nature of both dipoles and dipolarophiles. According to FMO theory

TABLE IX
STERESELECTIVE CYCLOADDITIONS OF AZOMETHINE YLIDES TO SYMMETRICAL ACYCLIC OLEFINS
 $R^1R^2C=NR^+-C^-R^3R^4 + EWGCH=CHWG$ (*E* or *Z*) \rightarrow stereoselective cycloadducts **248** (see **248** on p. 326)

R^1	R^2	R^3	R^4	R	2,3-	4,5-	Geometry	Reference
[MeOOCCH=CHCOOMe(<i>Z</i>)]								
Ph	H	COOMe	H	Li	<i>cis</i>	<i>cis</i>	<i>syn</i>	88JOC1384
Ph	H	H	COOR' ^a	R'' ^a	<i>cis</i>	<i>trans</i>	<i>anti</i>	85TL2775; 86CL1271; 87BCJ4067
Ph	H	Ph	CN ^b	H	<i>cis</i>	—	2,4- <i>syn</i>	86BCJ1809
PhCH=CR'(E) ^c	H	Ph	CN ^b	H	<i>cis</i>	—	2,4- <i>syn</i>	86BCJ1809
Ph	H	CN ^b	H	H	<i>cis</i>	—	—	85CL1601; 86BCJ1809; 87BCJ3359
Ph	H	Ph	H	H	<i>cis</i>	<i>cis</i>	<i>syn</i>	77CC768
[MeOOCCH=CHCOOMe(<i>E</i>)]								
$R^1/COOMe$								
COOM ^d	Me, Ph	COOM ^d	H	Zn, Cd	<i>cis</i>	<i>trans</i>	<i>syn</i>	86JCS(P1)1669
Ph	H	COOMe	H	Li	<i>cis</i>	<i>trans</i>	<i>syn</i>	88JOC1384
Ph	H	R ³ R ⁴ = CONH(CH ₂) ₃	H	H	<i>trans</i>	<i>cis</i>	<i>syn</i>	83TL4363
Ph	CN	PhCO	H	H	<i>trans</i>	<i>cis</i>	<i>syn</i>	86BCJ1809
[PhCOCH=CHCOPh(<i>E</i>)]								
COOZn	Me	COOZn	H	Zn	<i>cis</i>	<i>trans</i>	1,3- <i>syn</i>	86JCS(P1)1669

^a R' = Me, Et; R'' = Me, PhCH₂.

^b Isolated as 2-pyrrolines.

^c R' = H, Me.

^d M = Zn, Cd.

TABLE X
NONSTEREOSELECTIVE CYCLOADDITIONS OF AZOMETHINE YLIDES TO SYMMETRICAL ACYCLIC OLEFINS
 $R^1R^2C=NR^+-C^-R^3R^4 + EWGCH=CH EWG$ (*E* or *Z*) \rightarrow nonstereoselective cycloadducts **248** (see **248** on p. 326)

R ¹	R ²	R ³	R ⁴	R	Isomer ratio	Reference
[MeOOCCH=CHCOOMe(Z)]						
Ph	H	COOMe	H, Me, Ph	H	1.1 ~ 3	78TL2885; 80TL2461
H	H	COOMe	H	COMe	6.6	85H1107
Ph	H	H	H	H, <i>n</i> -Bu, PhCO	1.6 ~ 2.3	82TL2589; 83CPB3939; 84CL801; 85CPB1975; 86BCJ2537
[MeOOCCH=CHCOOMe(E)]						
Ph, <i>p</i> -PhC ₆ H ₄	H	H	COOR' ^a	Me, PhCH ₂ , <i>i</i> -Pr	1 ~ 1.6	79JOC255; 85TL2775; 87BCJ4067
Ph	H	COOMe	H	H	1.5	78TL2885
Ph	H	COOMe	PhCH ₂	H	—	80TL2461
H	H	COOMe	H	Me, COMe	1.8 ~ 3	85H1107
Ph	H	R ³ R = (CH ₂) ₄ , R ⁴ = COOMe			1	85TL2775
Ph	H	Ph	CN	H	3	86BCJ1809
PhCH=CH(<i>E</i>)	H	Ph	CN	H	2.5	86BCJ1809
PhCH=CMe(<i>E</i>)	H	Ph	CN	H	1.1	86BCJ1809
Ph	H	CN	H	H	1 ~ 2	85CL1601
SEt	H	H	H	<i>p</i> -NO ₂ C ₆ H ₄ CO	1	83CC210, 83JOC1554
Pip	H	H	H	PhCO	—	83CC210, 83JOC1554
Ph	H	H	Ph	Ph	4.1	71CC1187
Ph	H	H	H	R' ^b	1 ~ 1.5	82TL2589; 83CPB3939; 84CL801; 85CPB1975; 86BCJ2537; 87BCJ4079
1-Naph, 2-Py, <i>t</i> -Bu	H	H	H	H	1 ~ 3	86BCJ2537
R ¹ R = CH ₂ SCH ₂ , R ² = R ³ = H			H		1	87BCJ4079
[CNCH=CHCN(<i>E</i>)]						
Ph	H	H	H	H	1.4	84CL801; 86BCJ2537

^a R' = Me, Et.

^b R' = H, Me, *n*-Bu, PhCH₂, EtOOCCH₂, PhCO, PhCH₂CO.

(73JA7287; 73JA7301; 75ACR361), a dipole and a dipolarophile make bonds in a concerted cycloaddition process between the atoms possessing larger frontier orbital coefficients. If the cycloaddition is under the control of a HOMO (dipole)–LUMO (dipolarophile) interaction, the terminus of the dipole bearing a larger HOMO coefficient reacts with the terminus of the dipolarophile having a larger LUMO coefficient, and therefore the sites carrying smaller coefficients combine with each other. Therefore, regioselectivity for the given combination of dipole and dipolarophile may be estimated simply if the relative magnitudes of the frontier orbital coefficients of both dipole and dipolarophile are known.

Table XI collects the reaction examples for regioselective 1,3-dipolar cycloadditions of azomethine ylides to a variety of unsymmetrically substituted olefinic and acetylenic dipolarophiles. As these unsymmetrical dipolarophiles are in general sluggish in reactivity with azomethine ylides, this table would help readers find the ylide structures that exhibit high reactivity to these dipolarophiles. One may easily figure out which dipoles and dipolarophiles have sufficiently unsymmetrical frontier orbital coefficients. Among the electron-deficient dipolarophiles listed in this table, vinyl phenyl sulfone and methyl propiolate belong to the olefins that show very poor regioselectivity, indicating that the LUMO coefficients of the α and β carbons are almost equivalent. The azomethine ylides bearing an alkyl or an ester moiety as the only C substituent (e.g., ylide **41** or **91**) are not unsymmetrical enough at both termini to undergo highly regioselective cycloadditions.

The general structures of azomethine ylides that result in highly regioselective cycloadditions to a wide variety of dipolarophiles are as follows: (1) $R^1CH=NR^+-C^-(R^2)EWG$ bearing an aryl or alkyl moiety (R^1) at C-1 and an electron-withdrawing substituent (EWG: COOR', CN) at C-2. R^2 can be either H, R, or Ar. (2) $C(Y)R^1=NR^+-CH_2^-$ bearing a hetero group (Y: OR' or SR') and an alkyl or aryl substituent (R^1) at the same carbon C-1, and the other carbon C-2 is unsubstituted. (3) $ArCH=NR^+-CH_2^-$ bearing only one aryl group at C-1.

Two different dipoles sometimes can be generated from a common precursor and these two ylides show reverse regioselectivity in cycloadditions to methyl acrylate. Thus, the N-unsubstituted azomethine ylide **49** ($R^1 = Et$, $R^2 = Ph$), derived from α -(propylideneamino) phenylacetonitrile by the tautomerization route (Section II,C), undergoes a regioselective cycloaddition to methyl acrylate to give methyl 5-ethyl-2-phenyl-1-pyrrolinecarboxylate (**253**) after the elimination of LiCN (86BCJ1809). On the other hand, the same imine is activated by the action of LDA to generate N-lithiated dipole **252**, which is then trapped with methyl acrylate leading to

TABLE XI
REGIOSELECTIVE CYCLOADDITIONS OF AZOMETHINE YLIDES TO UNSYMMETRICAL DIPOLAROPHILES^a
 $R^1R^2C=NR^+-C^-R^3R^4 + \text{olefins} \rightarrow \text{cycloadducts } \mathbf{249}$ (see **249** on p. 326)

R^1	R^2	R^3	R^4	R	EWG	Reference
$[CH_2=CHCOOMe]$						
Ph	H	COOR	H	H	3-COOMe	80CC648; 86CL1271; 87BCJ4067
Ph	H	COR' ^b	H, Me	Li	3-COOMe	88JOC1384
Ph	H	COOMe	Me, Ph	H	3-COOMe	80TL2461
Ar ^c	H	COOMe	Ph	Na	3-COOMe	80CC648
Ph	H	CN	H	H, Li	3-COOMe	85CL1601; 86BCJ1809; 87BCJ3359
Ph	H	CN	Me	Li	3-COOMe	87BCJ3359
Et	H	CN	Ph	H	4-COOMe	86BCJ1809
Et	H	CN	Ph	Li	3-COOMe	87BCJ3359
PipCO	Ph	H	H	H	3-COOMe	84CL2041
COOCu, COOZn	Me, Ph	COOCu, COOZn	H	Cu, Zn	3-COOMe	79S150; 82JCS(P1)1827; 86JCS(P1)1669
	$R^1R = (CH_2)_m$ ($m = 3, 4$), $R^2 = R^3 = R^4 = H$				3-COOMe	82CPB3167
OMe, SMe	Me, 4-pentenyl	H	H	PhCH ₂	3-COOMe	83JOC4773
OMe, SMe	Ph	H	H	Me, H	3-COOMe	84JOC3314; 85H2489; 86JOC1997; 87JOC2523
OMe, SMe		$R^2R = (CH_2)_m$ ($m = 3, 4$), $R^3 = R^4 = H$			3-COOMe	83JOC4773
OMe	$R^2R = CH(OBn)(CH_2)_2$	H	H		3-COOMe	80JA7993; 85JOC2170
Ph	H	H	H	H	3-COOMe	81CL1213; 83CPB3939; 84CPB2878; 85CPB1975; 86BCJ2537, 86CL1113
$[CH_2=CHCOMe]$						
Ph	H	COOMe	H	Li	3-COMe	88JOC1384
COOCu	Me	COOCu	H	Cu	3-COMe	82JCS(P1)1827
SMe	Ph	H	H	H	3-COMe	85H2489; 86JOC1997; 87JOC2523
$[CH_2=CHCHO]$						
COOCu	Me	COOCu	H	Cu	3-CHO	82JCS(P1)1827

(continued)

TABLE XI (Continued)

R ¹	R ²	R ³	R ⁴	R	EWG	Reference
[CH₂=CHCN]						
Ph	H	COOMe	H	H, <i>i</i> -Pr	3-CN	88JOC1384
PipCO	Ph	H	H	H	3-CN	84CL2041
COOCu, COOZn	Me, Ph	COOCu, COOZn	H	Cu, Zn	3-CN	79S150; 82JCS(P1)1827; 86JCS(P1)1669
Ph	H	H	H	H	3-CN	86BCJ2537
RR ¹ = 2-(CH ₂) ₂ -4,5-di-EtO-C ₆ H ₂		COOMe	H		3-CN	83T369
[CH₂=CHSO₂Ph]						
COOZn	Ph	COOZn	H	Zn	3-SO ₂ Ph	86JCS(P1)1669
2-Py	H	H	H	Me	3-SO ₂ Ph	85JOC4006
[MeCH=CHCOOMe(<i>E</i>)]						
Ph	H	COOR' ^d	H, Me, <i>i</i> -Pr	Li	3-COOMe	88JOC1384
Ph	H	CN	H, Me, <i>i</i> -Pr	Li	3-COOMe	87BCJ3359
Et	H	CN	Ph	Li	3-COOMe	87BCJ3359
SMe	Ph	H	H	H	3-COOMe	85H2489; 87JOC2523
Ph	H	H	H	H	3-COOMe	84CL801; 86BCJ2537; 87JOC2523
[PhCH=CHCOOMe(<i>E</i>)]						
Ph	H	COOMe	H	Li	3-COOMe	88JOC1384
Ph	H	COOMe	H	PhCH ₂	3-COOMe	85TL2775
Ph	H	CN	H	Li	3-COOMe	87BCJ3359
SMe	Ph	H	H	H	3-COOMe	85H2489; 87JOC2523
Ph		R ² = H, R ³ = COOMe, R ⁴ R = (CH ₂) ₃			3-COOMe	85TL2775
Ph	H	H	H	H	3-COOMe	84CL801; 86BCJ2537
[CH₂=C(Me)COOMe]						
Ph	H	COOMe, CON(CH ₂) ₄	H, Me, <i>i</i> -Pr	Li	3-COOMe	88JOC1384
Ph	H	CN	H	Li	3-COOMe	87BCJ3359
Ph	H	CN	Me	Li	3-COOMe	87BCJ3359
Et	H	CN	Ph	Li	3-COOMe	87BCJ3359
SMe	Ph	H	H	H	3-COOMe	85H2489; 87JOC2523
Ph	H	H	H	H	3-COOMe	84CL801; 86BCJ2537

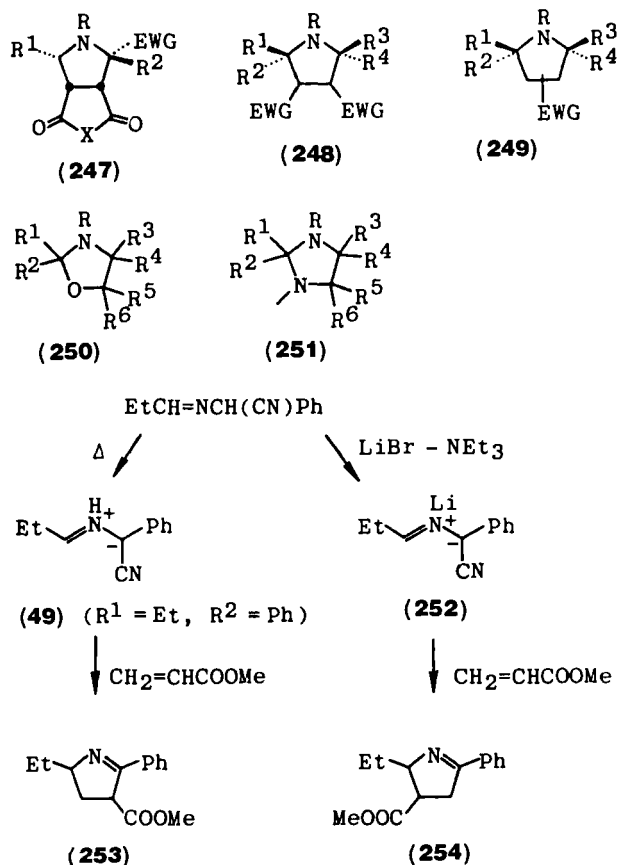
Ph	H	COOMe	[MeCH=CHCOMe(E)] H Li	3-COMe	88JOC1384
Ph	H	COOMe	[PhCH=CHCOMe(E)] H Li	COMe	88JOC1384
Ph	H	COOMe	[<i>p</i> -MeC ₆ H ₄ CH=CHCOPh(E)] H Li	COPh	88JOC1384
RR ¹ = 2-(CH ₂) ₂ -4,5-di-EtO-C ₆ H ₂ , R ² = H, R ³ = COOMe			[<i>p</i> -MeOC ₆ H ₄ CH=CHCOMe(E)] H	3-COMe	83T369
RR ¹ = 2-(CH ₂) ₂ -4,5-di-EtO-C ₆ H ₂ , R ² = H, R ³ = COOMe			[PhCH=CHCN(E)] H	3-CN	83T369
Ph	H	COOR	[PhCH=CHNO ₂ (E)] H Ph, Me	3-NO ₂	86CL1271; 87BCJ4067
RR ¹ = 2-(CH ₂) ₂ -4,5-di-EtO-C ₆ H ₂			[CH ₂ =CHOEt]	3-NO ₂	83T369
COOEt	H	H	H <i>p</i> -MeOC ₆ H ₄	3-OEt	85JOC2309
			[Cyclopentenone]		
COOEt	COOEt	H	H PhCH ₂	4-CO	84JCS(P1)2517
COOEt	COOEt	Ph	H Ph	4-CO	84JCS(P1)2517
			[HC≡CCOOMe]		
Ph	H	COOMe	Ph H	3-COOMe	82CC384
Ph	H	H	H PhCO	3-COOMe	81CL1213; 82TL2589; 83CPB3939
			[PhC≡CCOOMe]		
Ph	H	COOMe	Me, Et, Ph H	3-COOMe	80TL2461

^a Azomethine ylides that show poor regioselectivity to unsymmetrical dipolarophiles: CH₂=N⁺Me-CH⁻COOEt: CH₂=CHEWG (EWG = COOMe, SO₂Ph, Ph), PhCH=CHCOOMe, PhCH=C(COOMe)₂ (84TL1579; 85H1107; 86CL973; 87BCJ4067); CH₂=N⁺Me-CH⁻Ph: CH₂=CHSO₂Ph (87BCJ4079); MeCH=N⁺(CH₂Ph)-CH₂⁻: HC≡CCOOMe (85JOC4006); [(CH₂)₄CH=N⁺]-CH₂⁻: ArCH=CH₂, 2-cyclopentenone ethylene ketal, PhCH=CHOMe (85JOC2910); Ph(XMe)C=NR⁺-CH₂⁻ (X = O, S): HC≡CCOOMe (84JOC3314).

^b R' = OMe, N(CH₂)₄, NHBu-*t*.

^c Ar = Ph, *p*-MeOC₆H₄, *p*-ClC₆H₄, 2-furyl.

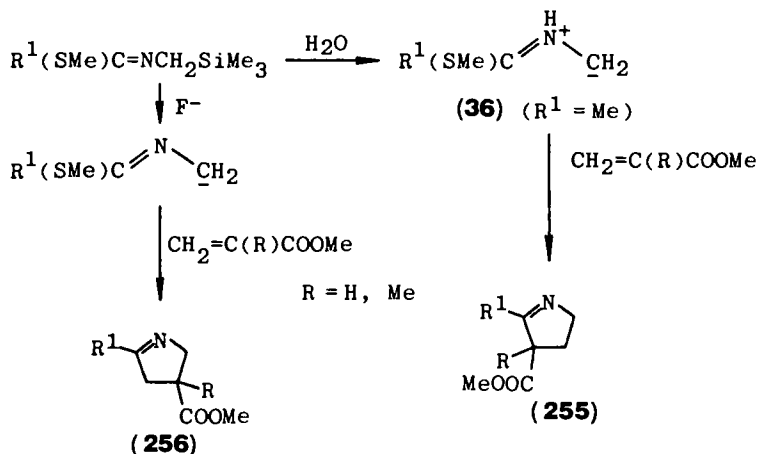
^d R' = OMe, N(CH₂)₄, NHBu-*t*.



regioisomeric 1-pyrroline **254** (87BCJ3359). This result indicates that the regioselection may be controlled by activating the ylide precursors.

Similar regiochemical control can be established by using α -silylalkyl-imines. When *N*-silylmethyl thioimides are treated with water in HMPA or DMF, *N*-unsubstituted ylides **36** are generated and trapped with methyl acrylate or methacrylate to give 1-pyrroline-3-carboxylates **255**. Treatment of thioimides with tetrabutylammonium fluoride in THF generates 2-azaallyl anions, whose trappings with the same olefins take place at the carbon substituted by the anion-stabilizing sulfur moiety to give rise to regioisomers of **255**, 1-pyrroline-4-carboxylates **256** (87JOC2523). Such an idea of regiocontrol is really important in organic synthesis, although only limited examples are known (84CL2041).

As carbonyl compounds and imines are extremely unsymmetrical dipolarophiles compared with carbon-carbon double and triple bonds, they show



exclusive stereoselectivity to the azomethine ylides, which are reactive to these dipolarophiles (Table XII). This type of reaction must be a typical HOMO (ylide)–LUMO (dipolarophile) interaction-controlled cycloaddition, and hence the terminus bearing the larger LUMO coefficient combines with the carbonyl or imine carbon.

E. REGIO- AND STEREOSELECTIVE CYCLOADDITIONS

Selective formation of a single isomer of many possible cycloadducts can be achieved when one geometry of azomethine ylide undergoes a cycloaddition to a dipolarophile in a regio- and stereoselective, and stereospecific, fashion. The azomethine ylide cycloadditions with such high diastereoselectivity could become a powerful strategy for the stereocontrolled synthesis of pyrrolidine derivatives. In this section some known examples of highly diastereoselective cycloadditions of azomethine ylide 1,3-dipoles are presented, and the origin of the diastereoselectivity is discussed.

Azomethine ylides whose nitrogen is included as a part of nitrogen heterocycles show a high stereo- and regioselectivity to aldehyde and imine dipolarophiles. The condensation of secondary amines, such as 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro- β -carboline, with pyridine-2-carbaldehyde generates azomethine ylides **88** and **257**, which are trapped by maleimides as *anti*-ylides (86CC602). If no dipolarophile is present, the resulting ylides, (*E,Z*)-**88** and **257**, undergo a regio-, endo-selective, and anti-specific cycloaddition to the pyridine-2-carbaldehyde used for ylide generation to furnish oxazolidine-fused cycloadducts **165** and **258**, respectively. Though aldehydes are very unsymmetric dipolarophiles, the dipoles **88** and

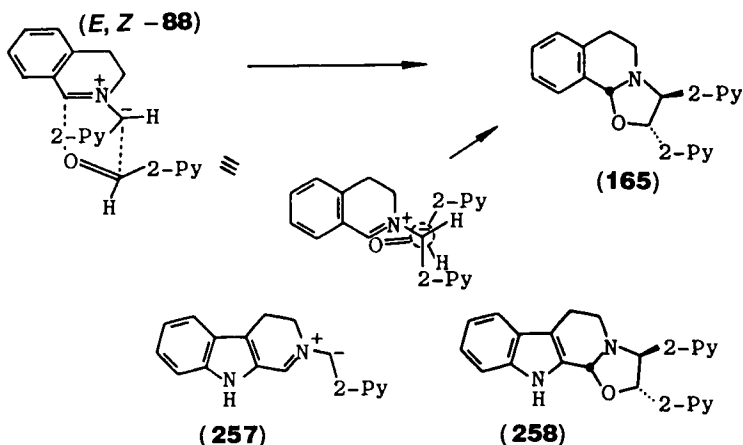
TABLE XII
REGIOSELECTIVE CYCLOADDITIONS OF AZOMETHINE YLIDES TO CARBONYLS AND IMINES
 $R^1R^2C=NR^+-C^--R^3R^4 + R^5CXR^6 \rightarrow$ cycloadducts **250** and **251** (see **250** and **251** on p. 326)

R^5CXR^6	R^1	R^2	R^3	R^4	R	Reference
Aldehydes and ketones						
PhCHO	Ph	H	H	H	Me	70JOC2069
ArCHO ^a	N(Me)Ph	Me, Et, <i>n</i> -Bu, Ph	H	H	H	85CL1411; 86JOC1997
PhCHO, 2-PyCHO	SMe	Et, <i>i</i> -Pr, Ph	H	H	H	87JOC2523
<i>m</i> -NO ₂ C ₆ H ₄ CHO	OMe	Ph	H	H	PhCH ₂	84JOC3314
2-PyCHO		RR ¹ = <i>o</i> -(CH ₂) ₂ C ₆ H ₄ , R ² = R ⁴ = H, R ³ = 2-Py				86CC602
MeCOPh, PhCOPh	SMe	Ph	H	H	H	87JOC2523
PhCOPh	Ph	Ph	H	H	Me	70JOC2069
Imines						
<i>p</i> -MeOC ₆ H ₄ CH=NMe	<i>p</i> -MeOC ₆ H ₄	H	COOMe	H		82LA2146
ArCH=NR ^b	RR ¹ = 2-(CH ₂) ₂ -4,5-di-MeO-C ₆ H ₂ , R ² = R ⁴ = H, R ³ = COOMe					82LA2146; 83T369
2-Phenyl-1-azirine	RR ¹ = 2-(CH ₂) ₂ -4,5-di-MeO-C ₆ H ₂ , R ² = R ⁴ = H, R ³ = COOEt					82LA2146
6,7-Dimethoxy-	RR ¹ = 2-(CH ₂) ₂ -4,5-di-MeO-C ₆ H ₂ , R ² = R ⁴ = H, R ³ = COOEt					82LA924
3,4-dihydroisoquinoline	RR ¹ = 2-(CH ₂) ₂ -4,5-di-MeO-C ₆ H ₂ , R ² = R ⁴ = H, R ³ = CN					82LA924

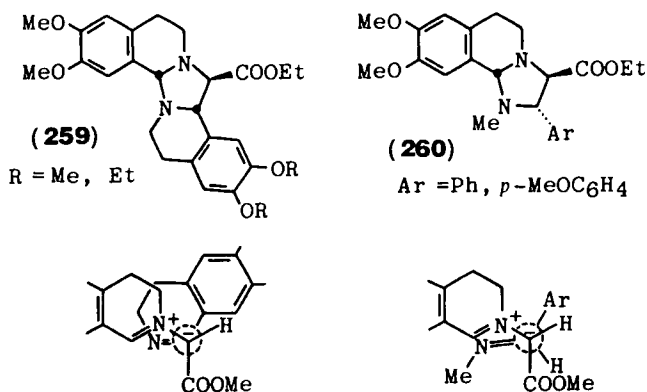
^a Ar = Ph, 2-tolyl, 2-Py, 2-thienyl, 2-furyl.

^b Ar = Ph, *p*-MeOC₆H₄, *p*-NO₂C₆H₄; R = Me, Ph.

257 are almost symmetric from a standpoint of their molecular orbital coefficients. As shown in the Newman-type projection, in which the bond being formed between the two atoms is circled with a dotted line, the exclusive regioselection, as well as the high endo selection, would have arisen from the sterically least hindered endo approach of the pyridine nucleus of the dipolarophile to the *anti*-ylides. Both regio- and stereoselectivity are sterically controlled in this cycloaddition.

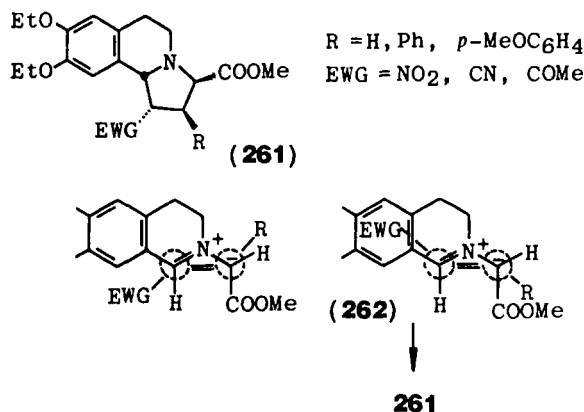


Similar *anti*-azomethine ylides **76** (EWG = COOR', R = MeO) bearing an ylide-stabilizing ester moiety are involved in the diastereoselective cycloadditions to 3,4-dihydroisoquinolines and *N*-(arylmethylene)methylamines to provide stereoselective imidazolidine-fused cycloadducts **259** and **260** (82LA924, 82LA2146). As imines and ylides **76** bear extremely different LUMO and HOMO coefficients on each termini, uniformly high regioselection is not surprising. endo-Approach of the dihydroisoquinolines to the



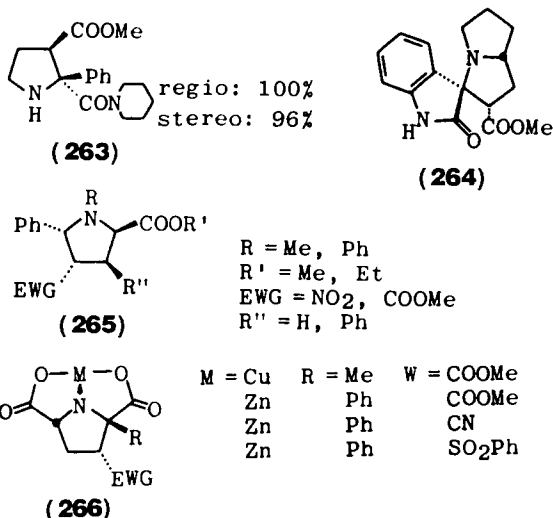
anti geometry of **76** is sterically less congested than the corresponding exo approach; in the approach leading to the stereostructure **260**, both N-methyl and aryl moieties of the (*E*)-*N*-(arylmethylene)methylamines become free from serious steric repulsion.

The same ylide **76** (EWG = COOMe, R = MeO) undergoes high regio- and stereoselective cycloadditions as an anti dipole to unsymmetric (*E*)-olefins, such as (*E*)- β -nitrostyrene, (*E*)- β -nitro(*p*-methoxy)styrene, (*E*)-3-phenylpropenenitrile, acrylonitrile, and (*E*)-4-(*p*-methoxyphenyl)-3-buten-2-one to give 1,10b-*cis*-2,3-*cis*-cycloadducts **261** (83T369). In all of these cases, the regioselectivity has been absolutely controlled due to the high degree of unsymmetry of the dipole **76** and the dipolarophiles. Between two regioselective approaches to **262**, one approach looks sterically very comfortable since both the olefinic substituents EWG and R are in the less crowded region. However, this is not the approach actually observed. Although the other approach involves an overlapping of EWG and R to the fused benzo and ylide-stabilizing COOMe moieties, respectively, just this is selectively favored. The attractive interactions between EWG and benzo groups and between R (except when R = H) and the ester are the driving forces that have overwhelmed the critical steric congestion.



Such attractive interaction based on secondary orbital interaction frequently determines the stereochemical course of 1,3-dipolar cycloadditions of azomethine ylides, producing sterically unfavorable stereoisomers as single products. In the following examples one may recognize some important secondary orbital interactions working between Ph and COOMe in **263** (84CL2041), between benzo and COOMe in **264** (86CC602), and doubly between Ph and EWG (NO_2 , COOMe) and COOR' and R'' (Ph) in **265** (86CL1271).

Secondary orbital interactions are often effective enough to determine the

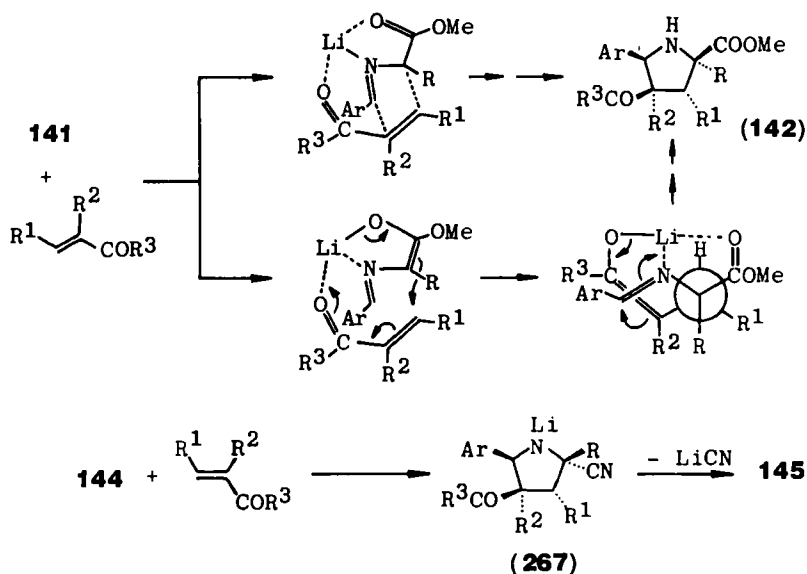


stereochemical path of 1,3-dipolar cycloadditions as shown above. As the major secondary orbital interaction works on the substituents of dipoles, the stereochemistry of cycloadditions depends upon the ylide configuration. A more reliable methodology to control the stereochemistry of cycloadditions has been recently developed. In the cycloadditions of N-metallated azomethine ylides with carbonyl-activated olefins, the carbonyl oxygen chelates the metal to allow the endo approach of olefinic dipolarophiles.

Thus, the N-metallated azomethine ylides **128** (M = Cu, Zn; R = Me, Ph), whose generation has been mentioned above (Section II,b), undergo ready cycloadditions with methyl acrylate, acrylonitrile, and phenyl vinyl sulfone giving rise to regio- and endo-selective cycloadducts **266** (86JCS(P1)1669). As an epimerization takes place during the cycloaddition or demetallation step, this highly selective synthetic methodology for pyrrolidines has some experimental limitation.

The N-metallated azomethine ylides having a wider synthetic potential are N-lithiated ylides **141**, derived from the imines of α -amino esters, lithium bromide, and triethylamine, and **144** from the imines of α -aminonitriles and LDA (Section II,G). Ester-stabilized ylides **144** undergo regio- and endo-selective cycloadditions, at room temperature, to a wide variety of unsymmetrically substituted olefins bearing a carbonyl-activating substituent, such as methyl acrylate, crotonate, cinnamate, methacrylate, 3-buten-2-one, (*E*)-3-penten-2-one, (*E*)-4-phenyl-3-buten-2-one, and (*E*)-1-(*p*-tolyl)-3-phenylpropenone, to give excellent yields of cycloadducts **142** (88JOC1384).

Although the reaction mechanism depends upon the nature of the reacting anionic species (as illustrated in the scheme), a chelation between the lithium and the carbonyl oxygen of the dipolarophiles may be responsible for the exclusive regio- and endo selectivity. This chelation is so rigid that the high endo selectivity as well as the enhanced reactivity remains even when the α substituent of the ylide is a sterically bulky isopropyl group and the β substituent an olefinic methyl. On the other hand, the selectivity of cycloadditions of ylides **141** is very poor when the olefin dipolarophiles bear a noncarbonyl substituent (e.g., acrylonitrile) or when *s-trans*-enones (e.g., 2-cyclopentenone) are used as dipolarophiles.



Equally selective cycloadditions occur, at -78°C , between cyano-stabilized ylides **144** and the above olefinic esters. As lithium cyanide is eliminated immediately after the cycloaddition is over, 4,5-*cis*-1-pyrrolines **145** are obtained (87BCJ3359). The stereochemistry of **145** arises from the initial regio- and endo-selective cycloadducts **267**.

This cycloaddition methodology utilizing N-lithiated azomethine ylides has some advantages. (1) The ylides can be generated *in situ* concurrently with or prior to cycloaddition. (2) The ylides are highly reactive toward a number of carbonyl-activated olefins. (3) Wide structural modification of ylides is possible. (4) The cycloadditions are perfectly diastereoselective. (5) No demetallation procedure is necessary. (6) No critical epimerization occurs even in the reactions of cyano-stabilized ylides **144**.

IV. Intramolecular Cycloadditions

Reactivity, regio- and stereoselectivity, and stereospecificity of the intermolecular cycloadditions of azomethine ylide 1,3-dipoles were reviewed in Section III. When one plans to utilize these reactions for a synthetic purpose, the following several points are important and have to be taken into consideration: (1) the reactivity of a particular azomethine ylide, (2) the geometry of the reacting dipoles, and (3) the stereochemical outcome expected in the cycloadditions. Then the proper combination between an azomethine ylide and a dipolarophile is selected.

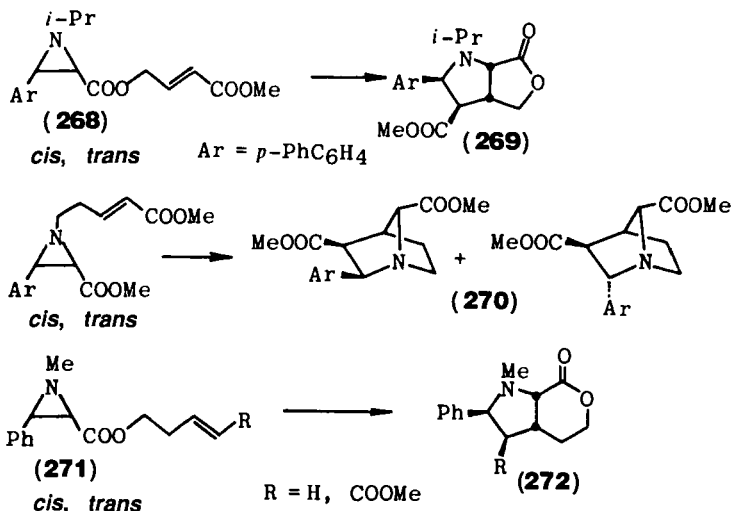
In many cases of intramolecular cycloadditions an enhanced reactivity of dipoles is observed. Accordingly, intramolecular cycloadditions have a synthetic advantage that nonactivated olefin dipolarophiles with alkyl substituent(s), which are very inert in the intermolecular versions, may serve as ylide traps. Both regio- and stereoselectivities are quite different from those observed in the intermolecular reactions. They mainly depend upon the length of the connecting chain that combines the dipole and dipolarophile and upon substituents on the chain.

A. YLIDES FROM THE AZIRIDINE ROUTE

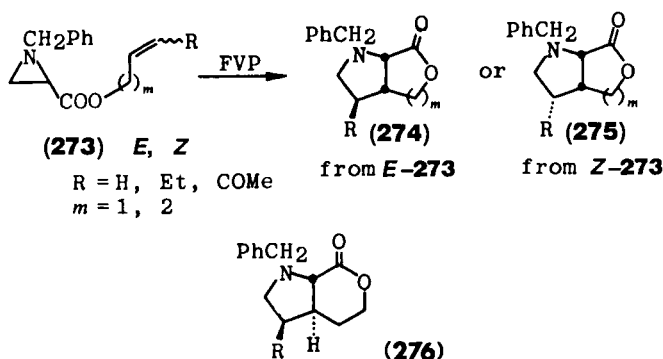
The first example of intramolecular cycloadditions using azomethine ylides has utilized aziridine derivatives bearing an ester-activated olefin as a dipole trap. Thus, heating either *cis*- or *trans*-aziridine **268** in benzene produces high yields of *cis*-fused [5.5]-bicyclic lactone **269** as a sole product (79JOC255). Exclusive formation of **269** indicates the selective participation of an anti-dipole in the stereospecific cycloaddition. This intramolecular cycloaddition is somewhat slower than expected and so intramolecular trapping of the kinetic ylide (*syn*-ylide) generated from *trans*-**268** has failed. The slow rate is evidenced by the competitive intermolecular cycloaddition using dimethyl acetylenedicarboxylate. When an olefinic chain is on the aziridine nitrogen, bicyclo systems **270** with a bridgehead nitrogen are produced.

Aziridine **271** ($R = \text{COOMe}$), having an activated olefin chain longer by one carbon, gives *cis*-fused [6.5]-cycloadduct **272** ($R = \text{COMe}$), and again *anti*-ylide has been selectively involved either from *cis*-**271** or *trans*-**271**. Though the azomethine ylides bearing an aryl at one carbon and an acyl at the other are inert to unactivated olefin dipolarophiles, the intramolecular version has overcome this difficulty. Thus, [6.5]-*cis*-fused cycloadduct **272** ($R = \text{H}$) is produced in high yield from the corresponding *cis*- or *trans*-aziridine **271** ($R = \text{H}$) (85JOC4114).

Ring opening of the aziridines **273** bearing an ester group as the only C

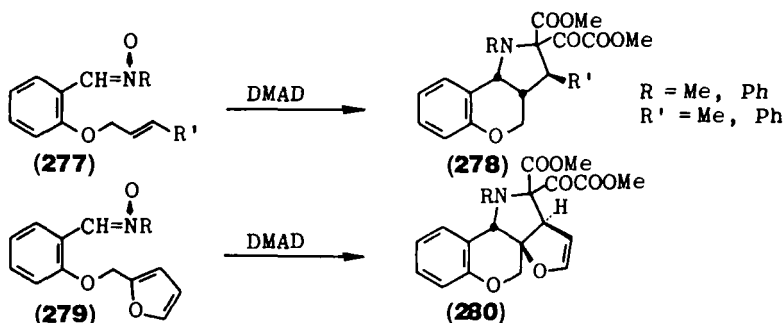


substituent is so difficult under the usual thermal conditions that a technique of flash vapor pyrolysis has been applied (85JOC2309). Mostly *cis*-fused [6.5]- and [5.5]-bicyclic lactones **274** and **275** are obtained from (*E*-**273** and (*Z*)-**273**, respectively, regardless of the existence of an olefin-activating substituent R (H, Et, COMe). Interesting is a rare example for the formation of *trans*-fused [6.5]-lactone **276** together with **275** (R = COMe, *m* = 2) in a 1:1 ratio.



The cycloadditions of nitrones with activated acetylenes provide 4-oxazolines, which readily ring open into highly stabilized azomethine ylides (Section II,H). This concept can be utilized in an intramolecular cycloaddition. Nitrones **277** undergo cycloadditions with dimethyl acetylenedicarboxylate (OMAD) to give cycloadducts **278** through the formation of intermediary azomethine ylides (84CL797). It is quite surprising that the

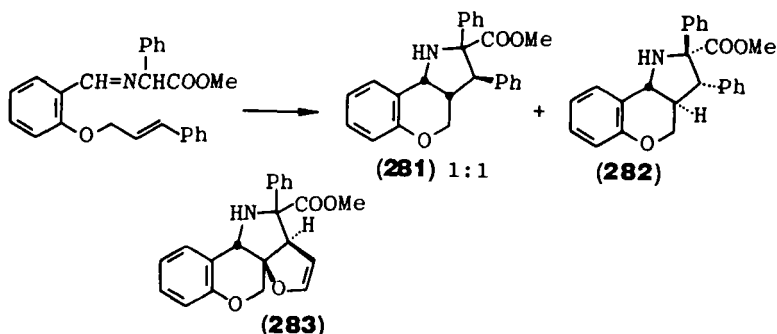
highly stabilized azomethine intermediates show sufficient reactivity toward the heteroaromatic furan ring. Thus, **279** reacts similarly with the acetylene to give intramolecular cycloadducts **280** in moderate yield.

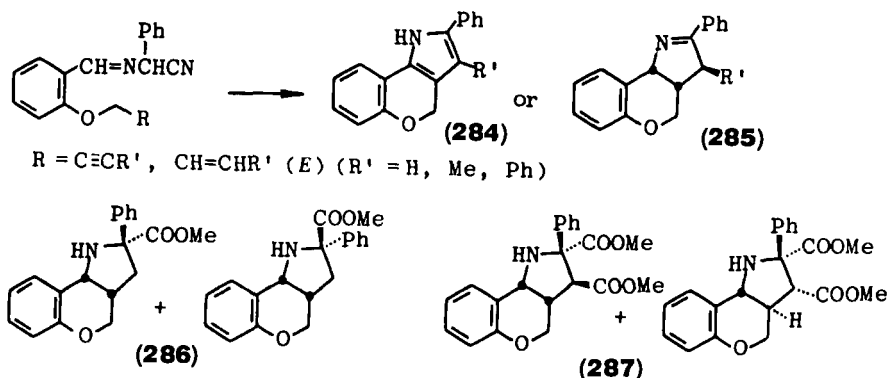


B. YLIDES FROM THE TAUTOMERIZATION ROUTE

Azomethine ylides generated by a thermal tautomerization of the imines of α -amino esters (Section II,C) react intramolecularly with acetylenes to give ring-fused pyrroles or pyrrolines after a spontaneous dehydrogenation and/or 1,5-sigmatropic ester shift (79CL1407). Intramolecular trapping of the same dipole with a cinnamyl olefin gives rise to a mixture of *cis*-**281** and *trans*-fused [6.5]-cycloadducts **282**. The *cis*-fused products **281** consist of a 1:1 mixture of the cycloadducts from the (*E,E*)- and (*E,Z*)-azomethine ylides, showing a low stereoselectivity with respect to the ylide geometry (81H1503). Internal trapping with inert furan dipolarophile leads to **283**, albeit in poor yield (84CL285).

The N-unsubstituted azomethine ylides derived from the imines of α -amino nitriles are intramolecularly trapped by acetylenes to give pyrroles





284 and by olefins to give pyrrolines **285**, after the elimination of the cyano moiety (83H2133). This former combination is especially convenient for the synthesis of fused-pyrrole derivatives.

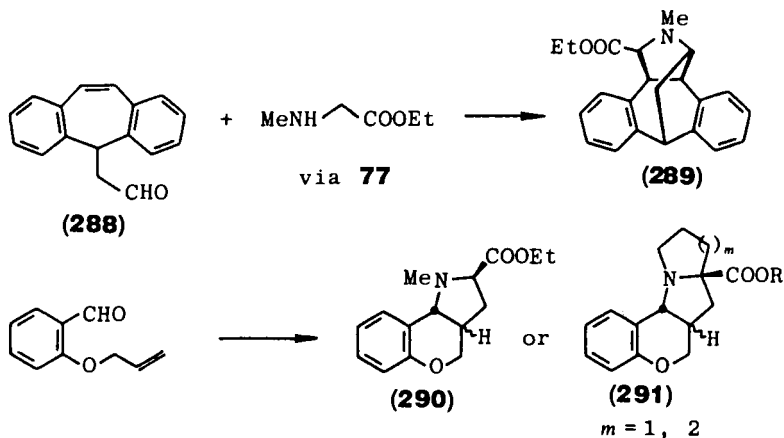
The N-unsubstituted azomethine ylide generated by the tautomerization route can be intramolecularly trapped by a nonactivated olefin leading to cis-fused [6.5]-cycloadduct **286**, and both (*E,E*)- and (*E,Z*)-ylides have participated in this cycloaddition (85T3547), since the furan cycloaddition leading to **283** is already known. Contrary to the nonselective participation of two ylide geometries, an exclusive trapping of the (*E,E*)-azomethine ylide by an ester-activated internal olefin has been achieved to give **287**, indicating that (*E,E*)-geometry would be the kinetic configuration of this ylide.

C. YLIDES FROM THE DEPROTONATION ROUTE

The simplest ylide generation method among the deprotonation route (Section II,D) consists of the condensation of N-substituted α -amino esters with carbonyl compounds. This procedure must be especially useful for utilization in intramolecular cycloadditions because the substrates for the cycloadditions are simply prepared *in situ* by reacting the carbonyl compounds (or secondary amines) bearing a trapping chain with secondary amines (or carbonyl compounds).

This idea was first demonstrated by Confalone. An aldehyde **288** was allowed to react with ethyl salcosinate under reflux in toluene and the resulting ylide was trapped by the internal olefin to give **289** in good yield (83JOC2994).

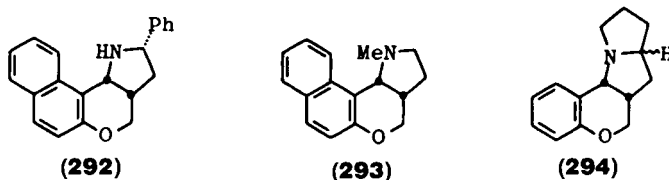
Advantages of this method include the possibility of wide structural variations from the single precursor as well as high yield formation of the cycloadducts. Starting from 2-(allyloxy)benzaldehyde, intramolecular cyclo-



adducts **290** (97%, *cis/trans* = 10), **291** ($m = 1$, R = Me, 98%, *c/t* = 2.5), and **291** ($m = 2$, R = Et, 99%, *c/t* = 11.5) are obtained by treating with ethyl salcosinate, methyl prolinatate, and ethyl pipercolinate, respectively (84JA7175). Further applications for the preparation of [5.5]- and [6.5]-ring-fused systems are known (86TL2695).

D. YLIDES FROM THE DECARBOXYLATION ROUTE

Although investigated only briefly, the generation of azomethine ylides by the decarboxylation route (Section II,E) and internal trapping are also made possible by a simple procedure. Heating 2-(allyloxy)naphthalene-1-carbaldehyde or *o*-(allyloxy)benzaldehyde with N-substituted or -unsubstituted α -amino acids in DMF for a short time provides a variety of *cis*-fused cycloadducts **292**–**294** (84CC180, 84CC182).



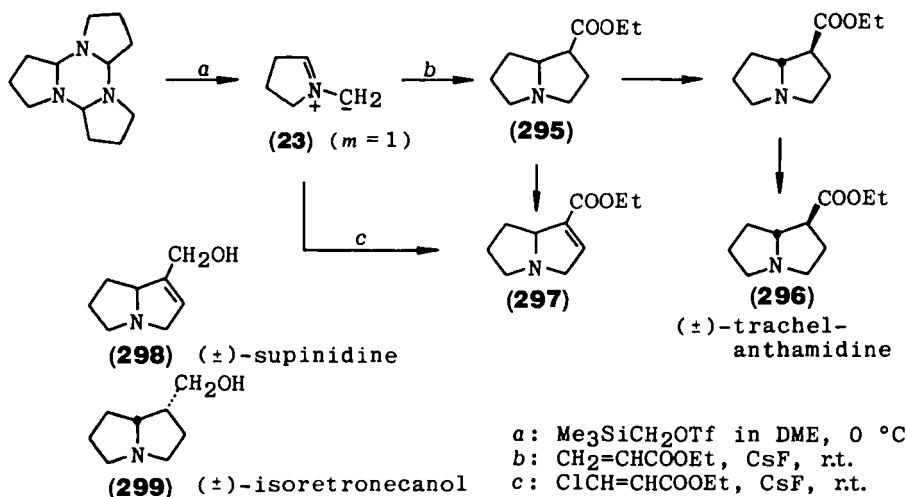
V. Natural Product Synthesis

Azomethine ylide cycloadditions have been utilized at times to construct the pyrrolidine skeletons involved in some natural products, mainly alkaloids, as separated rings or as part of fused-ring systems. Examples of

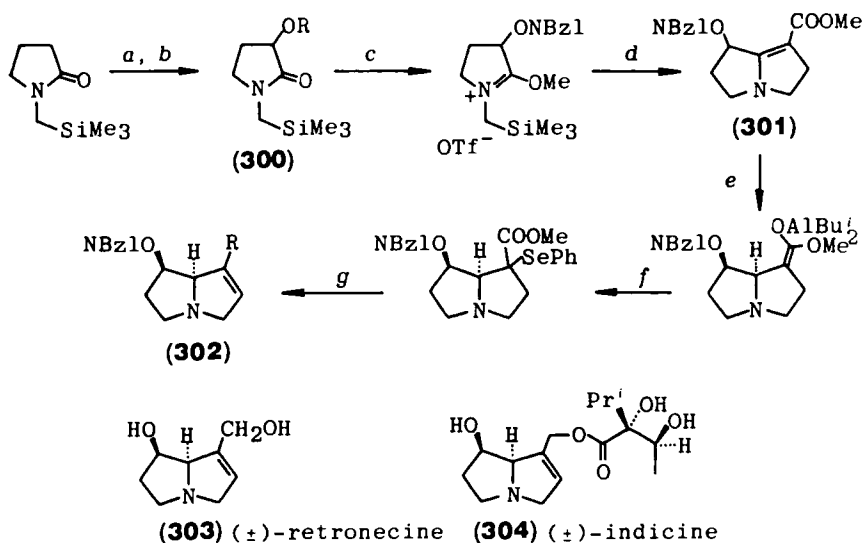
applications are quite limited. Except for the stereochemistry of the ring juncture in the cases of intramolecular cycloadditions, other stereochemical features such as regio- and stereoselectivity, and stereospecificity have not been fully utilized. We are confident that the cycloadditions of azomethine ylides will be more widely applied to the elaboration of alkaloid natural products with complex structures.

A. UTILIZATION OF INTERMOLECULAR CYCLOADDITIONS

Achiwa reported a short synthesis of pyrrolizidine derivatives by the cycloadditions using a nonstabilized azomethine ylide **23** ($m = 1$) (82CPB3167). When the trimer of 1-pyrroline is treated with a silylmethyl triflate, N-alkylation of the 1-pyrroline takes place. Then the resulting iminium salt is desilylated with fluoride ion in the presence of ethyl acrylate to give ethyl pyrrolizidine-1-carboxylate **295** as a mixture of stereoisomers (28%). After the epimerization of **295** with LDA, the ester moiety is reduced with lithium aluminum hydride in ether to provide (\pm)-trachelanthamidine (**296**). A double bond can be introduced into **295** by a sequence of phenylselenenylation at the 1-position, oxidation with hydrogen peroxide, and elimination of the selenyl moiety. The 1,2-dehydropyrrolizidine-1-carboxylate **297** is an excellent precursor of (\pm)-supinidine (**298**) and (\pm)-isoretronecanol (**299**). Though in poor yield, **297** is directly available by the reaction of **23** with ethyl 3-chloropropenoate.

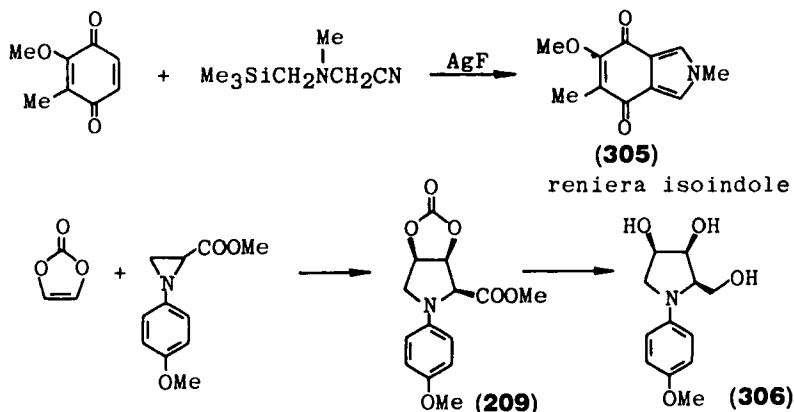


Retronecine, also a family of pyrrolizidine alkaloids, was synthesized by a similar strategy a few years before the work cited above (80JA7993). This synthesis was somewhat improved later (85JOC2170), and the improved synthesis is described below. *N*-Silylmethylpyrrolidine-2-one is α -deprotonated with LDA and treated with $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ to give 3-hydroxy-2-pyrrolidinone **300** ($\text{R} = \text{H}$). The 3-OH group is protected as the photosensitive *p*-nitrobenzyl ether **300** ($\text{R} = \text{NBzl}$). The carbonyl at the 2-position is then O-methylated with methyl triflate to form *N*-(silylmethyl)imidate salt as an azomethine ylide precursor. Desilylation with a fluoride ion and subsequent cycloaddition to methyl acrylate produce 1,7a-dehydropyrrolizidine-1-carboxylate **301** after the elimination of methanol from the initial cycloadduct. Stereoselective 1,4-reduction of **301** with diisobutylaluminum hydride (DIBAL) is followed by selenylation in a single step. An oxidation and elimination sequence gives rise to 1,2-dehydropyrrolizidine-1-carboxylate **302** ($\text{R} = \text{COOMe}$). Reduction of the ester **302** with DIBAL and subsequent deprotection (sunlamp in MeOH) lead to (\pm)-retronecine (**303**). (\pm)-Indicine (**304**), a monoester of retronecine, is readily derived from the mono O-protected alcohol **302** ($\text{R} = \text{CH}_2\text{OH}$) with trachelanthic acid acetone.



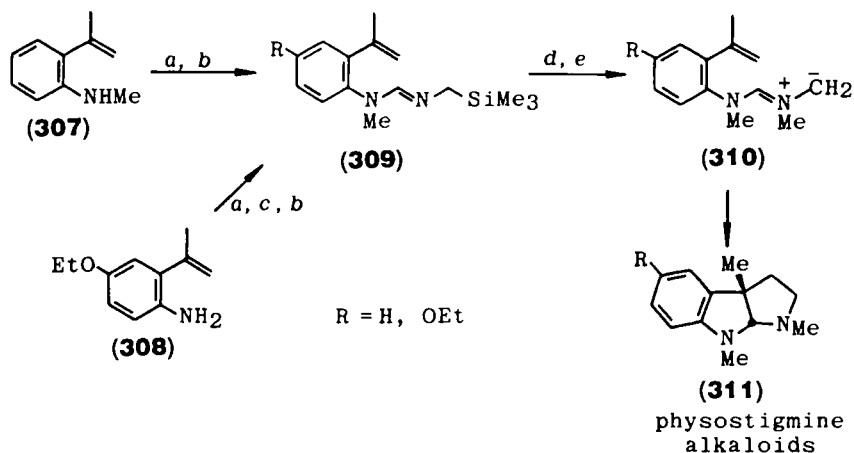
a: LDA, $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ in THF -45°C b: NaH in glyme,
p- $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{Br}$, 0°C c: MeOTf in CH_2Cl_2
d: $\text{CH}_2=\text{CHCOOMe}$, CsF, rt. e: DIBAL, -45°C f: PhSeCl,
 -78°C g: MCPBA in CH_2Cl_2 , -78°C

There are more examples of synthetic applications of intermolecular cycloadditions of azomethine ylides. The cycloaddition of 2-methoxy-3-methyl-*p*-benzoquinone with azomethine ylide **121**, generated from *N*-methyl-*N*-(trimethylsilylmethyl)aminoacetonitrile and AgF in acetonitrile, furnishes a reniera isoindole alkaloid **305** in 45% yield (85JOC4006). An α -mannosidase inhibitor, **306**, related to swainsonine has been prepared (85TL3747). Heating methyl 1-(*p*-methoxyphenyl)aziridine-2-carboxylate at 165°C in benzene generates ester-stabilized azomethine ylide **79** ($R^1 = H$, $R = p$ -methoxyphenyl, $R^2 = Me$). Smooth trapping of **79** with vinylencarbonate provides all *cis*-pyrrolidine-fused carbonate **209** (65%), whose reduction with lithium aluminum hydride gives triol **306**. An approach to the synthesis of kainic acid by intermolecular cycloadditions of azomethine ylides has been reported (84JCS(P1)2517).



B. UTILIZATION OF INTRAMOLECULAR CYCLOADDITIONS

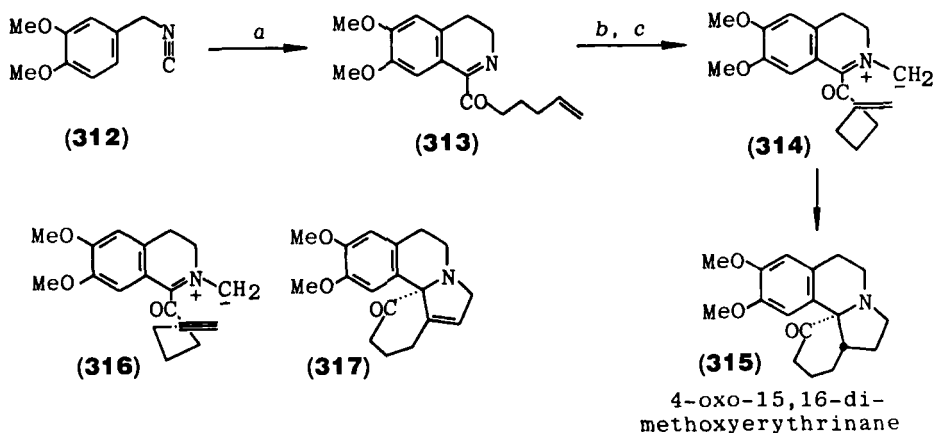
A new generation of amidinium ylides, discovered by Livinghouse and Smith, has been applied to synthesize physostigmine alkaloids **311** (83CC210, 83JOC1554; 85T3559). *N*-Formylation of *N*-methyl-2-isopropenylaniline (**307**) is followed by *O*-methylation with methyl triflate, and subsequent treatment with a silylmethylamine leads to amidine **309**. Similarly, *N*-formylation of 4-ethoxy-2-isopropenylaniline (**308**) is followed by *N*-methylation with NaH and MeI, *O*-methylation with methyl triflate, and amidination with the silylmethylamine to furnish amidine **309** ($R = OEt$). Amidines **309** are *N*-methylated with methyl triflate at 25°C in dichloromethane and the resulting formamidinium salts are treated with cesium fluoride or TBAF to generate azomethine ylides **310**. Internal trapping by



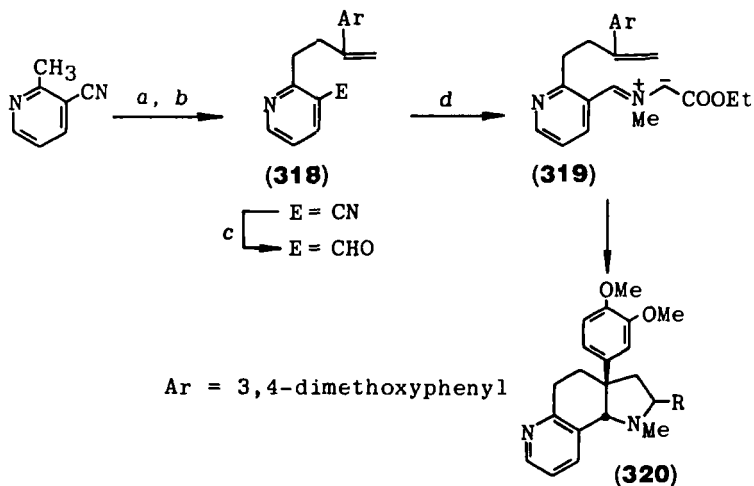
intramolecular cycloaddition of **310** gave physostigmine alkaloids, such as deoxyseroline (**311**) (R = H) and (±)-eserethole (**311**) (R = OEt).

The desilylation route (Section II,B) has also been used effectively to construct the skeletons of erythrina alkaloids (86JOC1159). Thus, reaction of 2-(3,4-dimethoxyphenyl)ethylisonitrile (**312**) with 5-hexenoyl chloride and subsequent cyclization in the presence of silver triflate produced 3,4-dihydroisindole **313**. N-Silylmethylation with a silylmethyl triflate and desilylation with a fluoride ion generates azomethine ylide **314**, whose intramolecular cycloaddition gives 4-oxo-15,16-dimethoxyerythrinane **315**. On the other hand, the azomethine ylide **316** bearing an acetylene trap, prepared by a similar method, gives **317**, which is then catalytically hydrogenated to **315**.

Confalone has successfully utilized the deprotonation route (Section II,D) for the synthesis of scelletium alkaloid A₄ (84JA7175). Deprotonation of 3-cyano-2-methylpyridine with lithium hexamethyldisilazane and subsequent alkylation with 3-bromo-2-(3,4-dimethoxyphenyl)propene provide **318** (R = CN). DIBAL reduction of this cyanide leads to aldehyde **318** (R = CN, which is needed for ylide generation by the deprotonation route). Heating **318** and ethyl sarcosinate at 180°C generates azomethine ylide **319**, whose cycloaddition gives rise to cycloadduct **320** (R = COOEt). Hydrolysis of the ester moiety with 1 *N* NaOH in THF/methanol to carboxylic acid is followed by a sequence of decarboxylation and reduction. Acid **320** (R = COOH) is heated with phenyl dichlorophosphate at 100°C and the resulting iminium product is reduced with sodium cyanoborohydride to provide (±)-scelletium alkaloid A₄ (**320**, R = H).



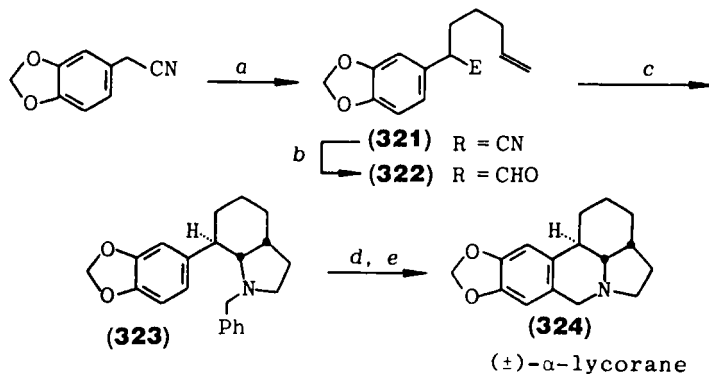
a: $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{COCl}$ in CH_2Cl_2 , rt. \rightarrow AgOTf , -20°C , NEt_3
b: $\text{Me}_3\text{SiCH}_2\text{OTf}$ in CH_2Cl_2 , rt. *c*: CsF in DME, 65°C



a: $\text{LiN}(\text{Me}_3\text{Si})_2$ in 10% HMPA / THF, -78°C *b*: 3-bromo-2-(3,4-dimethoxyphenyl)propene *c*: DIBAL, 0°C
d: $\text{MeNHCH}_2\text{COOEt}$ in xylene, 180°C (sealed tube)

The last example consists of the synthesis of lycorane skeletons by an intramolecular cycloaddition of the azomethine ylide generated by the decarboxylation route (Section II,E). Thus, 3,4-(methylenedioxy)phenylacetonitrile is deprotonated with LDA and then alkylated with 5-bromo-1-pentene

in HMPA/THF to give **321**, which is reduced with DIBAL to produce aldehyde **322**. Heating **322** and *N*-benzylglycine in toluene furnishes a single isomer of intramolecular cycloadduct **323**. Debenzylation of **323** by a catalytic hydrogenation followed by a cyclization with formaldehyde provides (\pm)- α -lycorane (**324**) (84TL4613).



a : LDA in HMPA / THF, 5-bromo-1-pentene, $-78^\circ\text{C} + \text{rt.}$
 b : DIBAL c : *N*-benzylglycine + $\text{HN}(\text{SiMe}_3)_2$, reflux
 in toluene d : $\text{HCOOH} / \text{MeOH}$, 10% Pd/C e : HCHO

VI. Conclusion

The chemistry of azomethine ylide 1,3-dipoles, especially that of acyclic azomethine ylides, has completely changed since 1978. Methods of generating azomethine ylides, which were seriously limited before then to the aziridine route (Section II,A) and the deprotonation route (Section II,D), have been much extended. New methods, such as the desilylation route (Section II,B), the tautomerization route (Section II,C), the decarboxylation route (Section II,E), the N-oxide route (Section II,F), and the N-metallation route (Section II,G), are now known and the types of azomethine ylides available have been widely expanded.

The previous empirical rule that only those azomethine ylides stabilized by at least one electron-withdrawing substituent can be generated smoothly has to be completely rewritten now. Nonstabilized azomethine ylides bearing no ylide-stabilizing substituent are now readily accessible and they are stable enough to be utilized in cycloadditions to a wide range of dipolarophiles without trouble. The desilylation route and the decarboxylation route effectively serve this purpose. N-Unsubstituted or even N-metallated azomethine ylides, tautomers of the corresponding imines or α -metallated

imines, are accessible through the desilylation, tautomerization, and N-metallation routes. Cycloadditions of these ylides provide N-unsubstituted cycloadducts, and the N-unsubstituted azomethine ylides bearing an eliminating group serve as synthetic equivalents of nonstabilized nitrile ylides. The nonstabilized azomethine ylides generated by the N-oxide route are exceptionally reactive, undergoing cycloadditions to nonactivated olefin dipolarophiles.

In general, stereoselectivity of the cycloadditions using N-unsubstituted azomethine ylides is much higher than that observed in the cycloadditions of N-substituted ylides. Although polymerization of activated olefin dipolarophiles or the formation of Michael adducts is found sometimes, cycloadditions of N-metallated azomethine ylides show extremely high stereo- and regioselectivities.

As shown in the application examples (Sections IV and V), the cycloadditions of azomethine ylides represent a powerful strategy in heterocyclic synthesis. The authors hope the readers see a generalized concept on the generation as well as the cycloaddition of azomethine ylides from this text, and hope that azomethine ylide 1,3-dipoles will be utilized more frequently as readily accessible reactive intermediates in the elaboration of complex target molecules.

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